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(54) Title: DIPEPTIDYLQUINAZOLONES AS ANTI-CANCER AGENTS

(57) Abstract

Quinazolines of formula (I) wherein R^1 is hydrogen or amino, or R^1 is alkyl, alkoxy or alkylthio each of up to 6 carbon atoms; or R^1 is aryl or aryloxy each of up to 10 carbon atoms; or R^1 is halogeno, hydroxy or mercapto; or R^1 is alkyl of up to 3 carbon atoms which bears one or more substituents selected from halogeno, hydroxy and alkanoylamino each of up to 6 carbon atoms; or R^1 is alkoxy of up to 3 carbon atoms which bears one or more substituents selected from hydroxy and alkoxy of up to 6 carbon atoms; wherein R^2 is hydrogen or alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, mercaptoalkyl, alkylthioalkyl, halogenoalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkanoylalkyl, carboxyalkyl, carbamoylalkyl or alkanoyl each of up to 6 carbon atoms; wherein Ar is phenylene or heterocyclene which is unsubstituted or which bears one or more substituents selected from halogeno, cyano, nitro, hydroxy, amino and carbamoyl and alkyl, alkoxy, halogenoalkyl, alkanoylamino, alkylthio and alkoxycarbonyl each of up to 6 carbon atoms; R^3 is the residue of a dipeptide in which the first, N-terminal amino acid residue thereof attached to the carbonyl group of COR^3 is an amino acid residue (a) in which A is a carbon-carbon single bond or an alkylene group of up to 5 carbon atoms and V and V' are each separately hydrogen, or alkyl, alkenyl or alkynyl each of up to 6 carbon atoms; and the second amino acid residue is of an α-amino acid or a pharmaceutically-acceptable salt, ester or amide thereof are of therapeutic value, particularly in the treatment of cancer.

$$-NHCH(CO_2H)-A-\overset{\overset{V}{|}}{\underset{\underset{V'}{|}}{C}}-CO- \quad \text{(a)}$$

Dipeptidylquinazolones as anti-cancer agents

This invention relates to novel anti-cancer agents and more
particularly it relates to quinazoline derivatives which possess
anti-cancer activity.

One group of anti-cancer agents comprises antimetabolites
05   having anti-folate activity, such as aminopterin and methotrexate.
A newer compound of this type which showed considerable promise in
clinical trials is known as CB3717 and is described and claimed in
United Kingdom Patent No. 2 065 653B. Despite its promising
activity against human breast, ovarian and liver cancer, however,
10   CB3717 shows symptoms of toxicity in humans, particularly in
relation to the liver and kidneys. Such adverse side effects are
reduced in compounds in which the 2-amino substituent of CB3717 is
either missing or is replaced by one of various alternative
substituents as described and claimed respectively in United
15   Kingdom Patents Nos. 2 175 903 and 2 188 319.

Compounds of this type are believed to act as anti-cancer
agents by inhibiting the enzyme thymidylate synthase which catalyses
the methylation of deoxyuridine monophosphate to produce thymidine
monophosphate which is required for DNA synthesis. The anti-cancer
20   activity of CB3717 and like compounds may be assessed _in vitro_ by
determining their inhibitory effect on that enzyme, and in cell
cultures by their inhibitory effect on cancer cell lines such as
the mouse lymphoma cell line L1210 and the human breast cancer cell
line MCF-7.

25   Antimetabolites such as aminopterin and methotrexate which are
inhibitors of enzymes which utilise folic acid derivatives have
also shown promise in the treatment of various allergic diseases
such as allergic rhinitis, atopic dermatitis and psoriasis.

We have now found that certain quinazoline derivatives not only
30   show a good level of activity, in particular in respect of their
ability to inhibit thymidylate synthase, but also have a different
mode of action from CB3717 and other related quinazoline derivatives
which have been described. Thus it is believed that CB3717 and more

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particularly its 2-methyl analogue, which is described and claimed
in UK Patent No. 2 188 319, owe anti-tumour activity to an
intracellular polyglutamate form but that the compounds of the
present invention act directly without undergoing a significant
05   degree of gamma-glutamylation. This alternative mode of action of
the compounds of the present invention provides the potential for
more precise control in the administration of the compounds to
cancer patients, deriving especially from a shorter period of
intracellular retention following the completion of administration
10   and a lack of dependence on polyglutamylation which may vary in
degree from one patient to another. Moreover, the replacement of
the L-glutamic acid residue of CB3717 by an alternative group in
the compounds of the present invention will confer different
physical properties thereby influencing the overall characteristics
15   of the compounds.

Accordingly the present invention comprises a quinazoline of
formula (I):-

$$ \text{(I)} $$

wherein R^1 is hydrogen or amino;
or R^1 is alkyl, alkoxy or alkylthio each of up to 6 carbon atoms;
or R^1 is aryl or aryloxy, each of up to 10 carbon atoms;
20   or R^1 is halogeno, hydroxy or mercapto;
or R^1 is alkyl of up to 3 carbon atoms which bears one or more
substituents selected from halogeno, hydroxy and alkanoylamino each
of up to 6 carbon atoms;
or R^1 is alkoxy of up to 3 carbon atoms which bears one or more
25   substituents selected from hydroxy and alkoxy of up to 6 carbon
atoms;
wherein R^2 is hydrogen or alkyl, alkenyl, alkynyl, hydroxyalkyl,
alkoxyalkyl, mercaptoalkyl, alkylthioalkyl, halogenoalkyl,
cyanoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,

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alkanoylalkyl, carboxyalkyl, carbamoylalkyl or alkanoyl each of up
to 6 carbon atoms;

wherein Ar is phenylene or heterocyclene which is unsubstituted or
which bears one or more substituents selected from halogeno, cyano,

05   nitro, hydroxy, amino and carbamoyl and alkyl, alkoxy,
halogenoalkyl, alkanoylamino and alkoxycarbonyl each of
up to 6 carbon atoms;

wherein R^3 is the residue of a dipeptide in which the first,
N-terminal amino acid residue thereof attached to the carbonyl

10   group of COR^3

$$-NHCH(CO_2H)-A-\overset{\overset{\textstyle V}{\textstyle |}}{\underset{\underset{\textstyle V'}{\textstyle |}}{C}}-CO-$$

is an amino acid residue $-NHCH(CO_2H)-A-\overset{V}{\underset{V'}{C}}-CO-$ in which A is a

carbon-carbon single bond or an alkylene group of up to 5 carbon
atoms and V and V' are each separately hydrogen, or alkyl, alkenyl
or alkynyl each of up to 6 carbon atoms; and the second amino acid

15   residue is of an α-amino acid but with one or more of the following
provisos:

(a) at least one of V and V' is other than hydrogen,

(b) the nitrogen atom of the second amino acid residue is
substituted by an alkyl, alkenyl or alkynyl group of up to 4 carbon

20   atoms, by an alkyl group of up to 3 carbon atoms which bears one or
more halogeno group substituents or a hydroxy group substituent, or
by an ethylene, trimethylene or tetramethylene group linked to the
α-carbon atom of the second amino acid residue, and

(c) the α-carbon atom of the second amino acid residue is fully

25   substituted;

wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms;

wherein R^5 is hydrogen or alkyl of up to 4 carbon atoms; and
wherein each of R^6, R^7 and R^8 is hydrogen or alkyl or alkoxy each
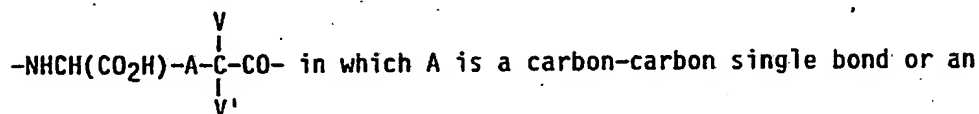of up to 4 carbon atoms; or is halogeno; the quinazoline

30   optionally being in the form of a pharmaceutically acceptable salt,
ester or amide thereof.

By way of contrast with the corresponding dipeptides of the
L,L configuration which are not one of: (a) substituted on the
carbon atom in the first amino acid residue adjacent to the amide

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linkage between the two residues, (b) N-substituted in the second
amino acid residue and (c) fully substituted at the α-carbon atom
in the second amino acid residue, the quinazoline dipeptides of the
present invention show a resistance to cleavage of the central

05   amide bond of the dipeptide _in vivo_. Thus, the existence of one or
more of these three forms of substitution adjacent to the amide
linkage leads to such a resistance to cleavage. Without limitation
to any specific theory, it is believed that the type of
substitution which is present in a quinazoline of the invention

10   adjacent to the amide linkage between the two residues of the
dipeptide achieves this effect through steric hindrance about that
linkage.

Although each of the forms of substitution may be present in
the compounds of the present invention, it is preferred that no

15   more than two of the forms and particularly only one is present,
substitution on the nitrogen atom of the second amino acid residue
being of most interest. In a preferred aspect of the invention,
therefore, R^3 is the residue of a dipeptide in which the first,
N-terminal amino acid residue thereof attached to the carbonyl

20   group of COR^3 is an amino acid residue

$$-NHCH(CO_2H)-A-\underset{\underset{V'}{|}}{\overset{\overset{V}{|}}{C}}-CO-$$ in which A is a carbon-carbon single bond or an

alkylene group of up to 5 carbon atoms and V and V' are each
separately hydrogen, or alkyl, alkenyl or alkynyl each of up
to 6 carbon atoms; and the second amino acid residue is of an

25   α-amino acid substituted on the nitrogen atom by an alkyl, alkenyl
or alkynyl group of up to 4 carbon atoms, by an alkyl group of up
to 3 carbon atoms which bears one or more halogeno group
substituents or a hydroxy group substituent, or by an ethylene,
trimethylene or tetramethylene group linked to the α-carbon atom

30   thereof, for example being the residue of an α-amino acid as
described hereinafter.

In this specification the terms alkyl, alkenyl, alkynyl and
alkylene include both straight and branched chain groups but
references to individual alkyl or alkylene groups such as "propyl"

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or "propylene" are specific for the straight chain group only. An
analogous convention applies to other generic terms. Moreover, the
numbering system used for the quinazoline nucleus is the
conventional one as shown below.
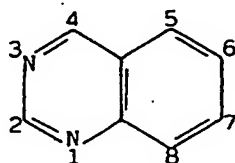
05   The amino-acid residues are designated in the standard manner
(Pure and Applied Chemistry, 1974, 40, 317 and European Journal of
Biochemistry, 1984, 138, 9). For the avoidance of doubt, however,
it should be noted that γ-glutamyl denotes the radical
$H_2NCH(CO_2H)CH_2CH_2CO-$ or $-NHCH(CO_2H)CH_2CH_2CO-$ according to the
10   context, the carbon atoms in these radicals being numbered from the
carbon atom of the α-carboxy group as position 1.

It will be observed that a quinazoline of the invention
contains at least one asymmetric carbon atom (present in the
peptide residue R^3) and can therefore exist in optically active
15   forms. It is to be understood that this invention encompasses the
various optically active forms of the quinazoline, it being a
matter of common general knowledge how such optically active forms
may be obtained by stereospecific synthesis or by separation of a
mixture of isomeric compounds. One isomer may however be of more
20   interest than another due to the nature of the activity which it
exhibits or due to superior physical properties, for example
aqueous solubility.

A suitable value for any of R^1, R^2, R^4, R^5, R^6, R^7 or R^8 when
it is alkyl, or for an alkyl substituent in Ar is, for example,
25   methyl, ethyl, propyl or isopropyl.

A suitable value for R^2 when it is alkenyl is, for example,
prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl,
hex-2-enyl, hex-5-enyl or 2,3-dimethylbut-2-enyl.

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A suitable value for R^2 when it is alkynyl is, for example, prop-2-ynyl, but-2-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl or hex-5-ynyl.

A suitable value for any of R^1, R^6, R^7 or R^8 when it is alkoxy,
05 or for an alkoxy substituent in Ar is, for example, methoxy, ethoxy or isopropoxy.

A suitable value for R^1 when it is alkylthio is, for example, methylthio or isopropylthio.

A suitable value for R^1 when it is aryl is, for example, phenyl
10 or tolyl.

A suitable value for R^1 when it is aryloxy is, for example, phenoxy or tolyloxy.

A suitable value for any of R^1, R^6, R^7 or R^8 when it is halogeno is, for example, fluoro, chloro, bromo or iodo.
15 A suitable value for R^1 when it is substituted alkyl is, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, chloromethyl, dichloromethyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, acetamidomethyl, 3-acetamidopropyl or propionamidomethyl.
20 A suitable value for R^1 when it is substituted alkoxy is, for example, 2-hydroxyethoxy, 4-hydroxybutoxy, 3-hydroxy-2-methyl- propoxy, 2-methoxyethoxy, 3-methoxypropoxy or 2-ethoxyethoxy.

A suitable value for R^2 when it is hydroxyalkyl, alkoxyalkyl, mercaptoalkyl or alkylthioalkyl is, for example 2-hydroxyethyl,
25 3-hydroxypropyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, 2-methoxypropyl, 2-mercaptoethyl, 3-mercaptopropyl, 2-methyl- thioethyl, 3-methylthiopropyl or 2-ethylthioethyl.

A suitable value for R^2 when it is halogenoalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl or dialkylaminoalkyl is, for example,
30 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 3-fluoropropyl, 3-chloropropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 2-aminoethyl, 3-aminopropyl, 3-amino-2-methylpropyl, 2-methylaminoethyl, 2-dimethylaminoethyl, 2-ethylaminoethyl, 2-diethylaminoethyl, 3-methylaminopropyl or 3-dimethylaminopropyl.

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A suitable value for R^2 when it is alkanoylalkyl, carboxyalkyl, carbamoylalkyl or alkanoyl is, for example, acetonyl, 2-acetylethyl, propionylmethyl, 2-propionylethyl, 3-acetylpropyl, 4-acetylbutyl, carboxymethyl, 2-carboxyethyl, carbamoylmethyl, acetyl, propionyl

05   or butyryl.

A suitable value for Ar when it is phenylene is, for example, 1,3- or particularly 1,4-phenylene.

A suitable value for Ar when it is heterocyclene is, for example, a 5-membered or 6-membered aromatic (that is, fully

10   unsaturated) heterocyclene diradical which contains up to 2 heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur, for example thienylene, pyridylene, pyrimidinylene, thiazolylene or oxazolylene. Of particular interest are compounds in which Ar is pyrimidinylene, particularly pyridylene or

15   especially phenylene.

A suitable halogeno, halogenoalkyl, alkanoylamino or alkoxycarbonyl substituent in Ar is, for example, fluoro, chloro, bromo, iodo, fluoromethyl, difluoromethyl, trifluoromethyl, acetamido, propionamido, isopropionamido, methoxycarbonyl,

20   ethoxycarbonyl or isobutoxycarbonyl.

A suitable level of substitution in Ar, where substitution is present, is three substituents, particularly two substituents or especially one substituent; and one or two substituents may conveniently be at positions adjacent to the atom bonded to the

25   group $-COR^3$, halogeno substituents such as fluoro being preferred.

The first amino acid residue of R^3 is and the second amino acid residue of R^3 may be of an α-amino acid in which the α-carbon atom is asymmetric, i.e. this carbon atom is bonded to four groups or atoms which differ from each other, one of which is a carboxy group

30   and another of which contains a grouping $-\overset{|}{N}-$ bonded to the carbon atom. In the case where the second amino acid residue has an α-carbon atom which is fully substituted none of the four bonds to the α-carbon atom joins it to a hydrogen atom, although two of the substituents may be identical so that the α-carbon atom is not

35   asymmetric.

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The first amino acid residue of the peptide residue R^3 may be
of the L- or D-configuration at its asymmetric α-carbon atom and
the second amino acid residue may similarly be of either
configuration at its α-carbon atom when that is asymmetric.
05   Conveniently, however, it is preferred that the first amino acid
residue, and the second amino acid residue also where appropriate,
is of the L-configuration. It will be appreciated that when both V
and V' are other than hydrogen but are different groups then the
carbon atom to which they are attached will also be asymmetric,
10   giving rise to _erythro_ and _threo_ forms for the amino acid providing
the first residue, both of which can exist as optically active
isomers.

Although the compounds of the present invention can exist as a
mixture of stereoisomers it is preferred that they are resolved
15   into one optically active isomeric form. Such a requirement
complicates the synthesis of the compounds and it is preferred
therefore that they contain as few asymmetric carbon atoms as
possible consistent with achieving the desired activity. Thus, for
example, when one of V and V' is other than hydrogen, the presence
20   of an additional asymmetric carbon atom will be avoided if both V
and V' are other than hydrogen and are identical groups. In many
cases, however, there will be two asymmetric carbon atoms in R^3, as
discussed hereinbefore, and the preferred L,L-quinazoline dipeptide
is conveniently substantially free from the D,D-dipeptide, and
25   conveniently it is also substantially free from the L,D and
D,L-dipeptides. In its preferred form, therefore, the dipeptide is
substantially free of all of the other three isomeric forms. The
term "substantially free" is used herein to indicate the presence
of no more than 20% and especially no more than 10% by weight of
30   the other isomer or isomers referred to.

A suitable value for R^3 is a dipeptide residue in which the

first, N-terminal amino acid residue $-NHCH(CO_2H)-A-\overset{\displaystyle V}{\underset{\displaystyle V'}{C}}-CO-$ is linked

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to a second amino acid residue $-\overset{\overset{\displaystyle X}{|}}{N}-\overset{\overset{\displaystyle Y}{|}}{\underset{\underset{\displaystyle Y'}{|}}{C}}-CO_2H$ to provide a group R^3 of

the formula $-NH-CH(CO_2H)-A-\overset{\overset{\displaystyle V}{|}}{\underset{\underset{\displaystyle V'}{|}}{C}}-CON-\overset{\overset{\displaystyle Y}{|}}{\underset{\underset{\displaystyle Y'}{|}}{C}}-CO_2H$ with $\overset{X}{|}$ on the N

in which A, V and V' are as defined hereinbefore;

X is hydrogen, an alkyl, alkenyl or alkynyl group of up

05 to 4 carbon atoms or a C_{1-3} alkyl group substituted by one or more

halogeno groups or a hydroxy group;

Y is hydrogen or alkyl, alkenyl or alkynyl each of up

to 6 carbon atoms;

or X and Y together are a group $(CH_2)_n$ where n is 2, 3 or 4;

10 and Y' is hydrogen or alkyl, alkenyl or alkynyl each of up

to 6 carbon atoms;

or Y' is alkyl of up to 6 carbon atoms which bears one or more

substituents selected from amino, carboxy, hydroxy and mercapto;

or Y' is phenyl or benzyl; but with the proviso that one or

15 more of the following is the case:

(a) at least one of V and V' is other than hydrogen.

(b) X is other than hydrogen, and

(c) Y and Y' are each other than hydrogen.

An alternative value for R^3 is a dipeptide residue in which the

20 first, N-terminal amino acid residue $-NH-CH(CO_2H)-A-\overset{\overset{\displaystyle V}{|}}{\underset{\underset{\displaystyle V'}{|}}{C}}-CO-$, A, V

and V' being as defined hereinbefore, is linked to a second amino

acid residue which is other than those of the type

$-N(X)C(Y)(Y')-CO_2H$ described hereinbefore and which corresponds to

the residue of a naturally occurring amino acid or such an amino

25 acid which is N-substituted by an alkyl, alkenyl or alkynyl group

of up to 4 carbon atoms, or by a C_{1-3} alkyl group substituted by

one or more halogeno groups or a hydroxy group.

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A suitable value for A is a carbon-carbon single bond or preferably an alkylene group of 2 carbon atoms or particularly 1 carbon atom, for example CH_2CH_2 and especially CH_2.

A suitable value for V or V' when it is alkyl, alkenyl or
05   alkynyl is as described hereinbefore for such groups R^2 but especially methyl.

It is preferred that when V is other than hydrogen V' is also other than hydrogen, conveniently being the same as V. One group of compounds of particular interest contains a grouping A-CV(V') in
10   which V and V' are each hydrogen and another group of compounds of some interest contains a grouping A-CV(V') in which V and V' are each the same alkyl group, particularly a methyl group. Hence, in many compounds the grouping A-CV(V') may conveniently be a group A' which is an alkylene group of up to 6 carbon atoms, for example
15   of 1, 3 or particularly 2 carbon atoms, for example CH_2, $CH_2CH_2CH_2$ and especially CH_2CH_2 or, particularly when the nitrogen atom of the second amino acid residue is not substituted, $CH_2CH(CH_3)$ and especially $CH_2C(CH_3)_2$.

A suitable value for X when it is alkyl, alkenyl or alkynyl of
20   up to 4 carbon atoms is as described hereinbefore for such groups R^2, particularly prop-2-enyl, prop-2-ynyl and especially the C_{1-3} alkyl groups such as ethyl and particularly methyl. A suitable value for X when it is a halogeno substituted or hydroxy substituted C_{1-3} alkyl group is as described hereinbefore for such
25   groups R^1, the halogeno substituents of choice being fluoro groups, with 2-substituted ethyl groups being of particular interest in the case of hydroxy substitution and substituted ethyl and especially methyl groups being of particular interest in the case of halogeno substitution. X is preferably a group other than hydrogen and this
30   may conveniently be one of the monovalent aliphatic hydrocarbon groups as just described or to a lesser extent, together with Y, a group $(CH_2)_n$ where n is 2, 4 or especially 3.

A suitable value for either of Y and Y' when it is alkyl is as described hereinbefore for such groups R^1, i.e. propyl and
35   isopropyl, ethyl, and especially methyl.

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A suitable value for either of Y and Y' when it is alkenyl or alkynyl is as described hereinbefore for such groups R^2 but particularly prop-2-enyl and prop-2-ynyl.

A suitable value for Y' when it is a substituted alkyl group is a group which carries one substituent only, particularly a carboxy group, with that substituent conveniently being on a terminal carbon atom of the alkyl group. Such groups are of particular interest among the various possibilities for Y'. Of especial interest are alkyl groups of up to 3 carbon atoms, i.e. methyl, ethyl, propyl and isopropyl, although larger groups can be of interest, particularly when branched. Preferred groups Y' of this type are thus CH_2CO_2H or $CH_2CH_2CH_2CO_2H$, particularly $CH_2CH(CH_3)CO_2H$ or $CH(CH_3)CH_2CO_2H$ and especially $CH_2CH_2CO_2H$.
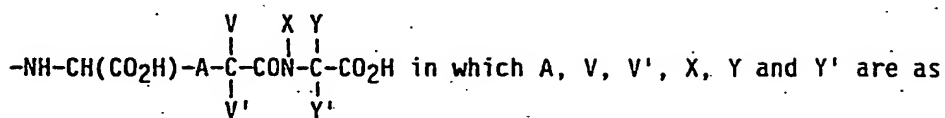
Examples of naturally occurring amino acids $H_2NCH(Y')CO_2H$ containing a group Y' which may be present in the group R^3 of the quinazolines of the present invention either as such or in N-substituted, for example N-methyl substituted, form (these groups Y' being either a group as specifically discussed above or other forms of group) are alanine (Y' = CH_3), arginine (Y' = $(CH_2)_3NHC(NH_2)=NH$), aspartic acid (Y' = CH_2CO_2H), cysteine (Y' = CH_2SH), glutamic acid (Y' = $CH_2CH_2CO_2H$), isoleucine (Y' = $CH(CH_3)CH_2CH_3$), leucine (Y' = $CH_2CH(CH_3)CH_3$), ornithine (Y' = $(CH_2)_3NH_2$), phenylalanine (Y' = $CH_2C_6H_5$), serine (Y' = CH_2OH) and valine (Y' = $CH(CH_3)_2$).

Examples of amino acids $H_2NCH(Y')CO_2H$ which are not naturally occurring which contain groups Y' that may be present in the group R^3 of the compounds of the present invention either as such or in N-substituted, for example N-methyl substituted, form are norvaline (Y' = $CH_2CH_2CH_3$), norleucine (Y' = $(CH_2)_3CH_3$), 2-phenylglycine (Y' = C_6H_5) and tert-leucine (Y' = $C(CH_3)_3$).
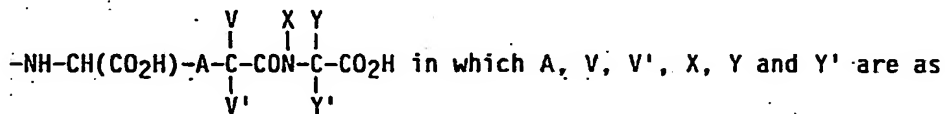
The most preferred groups R^3 contain a second amino acid residue which is N-substituted, particularly N-methyl substituted.

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Such groups R^3 will therefore often be of the formula

$$
\begin{array}{ccc}
& V & X\ Y \\
& | & |\ | \\
-NH-CH(CO_2H)-A-C-CON-C-CO_2H & & \text{in which A, V, V', X, Y and Y' are as} \\
& | & \ | \\
& V' & Y'
\end{array}
$$

defined hereinbefore but with X being other than hydrogen,
particularly being methyl, and preferably with Y being hydrogen and

05   conveniently with V and V' also being hydrogen. Alternatively,
somewhat less preferred groups R^3 contain a first amino acid
residue in which at least one and preferably both of V and V' are
other than hydrogen or contain a second amino acid residue in which
the α-carbon atom is fully substituted, one of the substituent

10   groups preferably being methyl in each case, both of such
possibilities optionally but less preferably being present. Such
groups R^3 will therefore often be of formula

$$
\begin{array}{ccc}
& V & X\ Y \\
& | & |\ | \\
-NH-CH(CO_2H)-A-C-CON-C-CO_2H & & \text{in which A, V, V', X, Y and Y' are as} \\
& | & | \\
& V' & Y'
\end{array}
$$

defined hereinbefore but with V and V' each being other than

15   hydrogen, for example each being methyl and/or with Y and Y' each
being other than hydrogen, for example each being methyl, and
preferably with X being hydrogen.

Groups R^3 of particular value have the formula

$$-NHCH(CO_2H)-A'-CON(X)CH(Y')-CO_2H$$

20   in which A' is an alkylene group of up to 6 carbon atoms, for
example being $CH_2CH(CH_3)$, $CH_2C(CH_3)_2$, $CH_2CH_2CH_2$ or CH_2CH_2, X is as
defined hereinbefore and Y' is methyl, ethyl, propyl,
hydroxymethyl, phenyl or benzyl, and especially have the formula

$$-NHCH(CO_2H)-A'-CON(CH_3)CH(CO_2H)(CH_2)_m-CO_2H$$

25   in which A' is as just defined, for example being $CH_2CH(CH_3)$,
$CH_2C(CH_3)_2$, particularly $CH_2CH_2CH_2$ and especially CH_2CH_2 and m is
1, particularly 3 and especially 2.

Specific examples of R^3 are the residues of the dipeptides
γ-glutamyl-α-methylalanine, γ-4-methylglutamylglutamic acid,

30   γ-4,4-dimethylglutamylglutamic acid, γ-glutamylproline,
γ-glutamyl-N-methylglycine, γ-glutamyl-N-methyl-alanine,

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γ-glutamyl-N-methyl-aspartic acid, particularly
γ-glutamyl-N-methyl-2-aminoadipic acid and most especially
γ-glutamyl-N-methyl-glutamic acid, preferably the L,L forms thereof
or the L form in the case of γ-glutamyl-N-methylglycine.

05   A suitable pharmaceutically-acceptable salt form of a
quinazoline of the invention is, for example, an acid addition salt
with an inorganic or organic acid, for example hydrochloric,
hydrobromic, trifluoroacetic or maleic acid; or an alkali metal,
for example sodium, an alkaline earth metal, for example calcium,

10   or ammonium, for example tetra(2-hydroxyethyl)ammonium, salt.

A suitable pharmaceutically-acceptable ester form of a
quinazoline of the invention is, for example, an ester with an
aliphatic alcohol of up to 6 carbon atoms, for example a methyl,
ethyl or _tert_-butyl ester.

15   A suitable pharmaceutically-acceptable amide form of a
quinazoline of the invention is, for example, an unsubstituted
amide of the form $-CONH_2$ or particularly a benzyl substituted amide
of the form $-CONHCH_2C_6H_5$.

It is to be understood that R^3 may contain several carboxy

20   groups. When it comprises three carboxy groups as is the case for
various of the preferred dipeptide residues R^3, for example when R^3
consists of two glutamic acid residues, a salt or ester may be
mono-acid-di-salt or -ester or -amide or it may be a
di-acid-mono-salt or -ester or -amide or even a tri-salt or -ester

25   or -amide.

Particularly preferred values for the various symbols R^1 to R^8
and Ar individually are as expressed for the preferred quinazolines
described hereinafter. Moreover, in the case of R^4, R^5, R^6 and R^8
compounds in which each of these is hydrogen are of especial

30   interest. With R^7, however, compounds in which this is other than
hydrogen, for example being one of the groups methoxy, fluoro and
chloro and particularly an alkyl group such as methyl, are also of
especial interest.

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A preferred quinazoline of the invention has the formula stated
above wherein R^1 is halogeno- or hydroxy-substituted alkyl or
particularly hydrogen, amino, alkyl or alkoxy, especially
fluoromethyl, hydroxymethyl, hydrogen, amino, methyl, ethyl or
05   methoxy;
wherein R^2 is methyl, ethyl, prop-2-enyl, prop-2-ynyl,
2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl or acetonyl;
wherein Ar is 1,4-phenylene, 2-fluoro-1,4-phenylene or
2,6-difluoro-1,4-phenylene;
10   wherein R^3 is the residue of the dipeptide γ-glutamyl-N-
methyl-2-aminoadipic acid or γ-glutamyl-N-methyl-glutamic acid,
preferably in the L,L form;
wherein R^4 is hydrogen or methyl;
wherein R^5 is hydrogen;
15   wherein R^6 is hydrogen or chloro;
wherein R^7 is hydrogen, methyl, fluoro or chloro, and
wherein R^8 is hydrogen, methoxy or chloro.
An especially preferred quinazoline of the invention has the
formula stated above wherein R^1 is methyl;
20   wherein R^2 is methyl, ethyl or preferably prop-2-ynyl;
wherein Ar is 1,4-phenylene or 2-fluoro-1,4-phenylene;
wherein R^3 is γ-L-glutamyl-N-methyl-L-glutamic acid;
wherein R^4 is hydrogen or methyl;
wherein R^5 is hydrogen;
25   wherein R^6 is hydrogen or chloro;
wherein R^7 is hydrogen, methyl, methoxy, fluoro or chloro and
wherein R^8 is hydrogen, methyl, methoxy or chloro.
Other quinazolines of the invention of particular interest have
the values of R^1, R^2, R^4 to R^8 and Ar in combination as indicated
30   above but with R^3 having any value as indicated hereinbefore.
However, specific particularly preferred quinazolines of the
invention are:
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
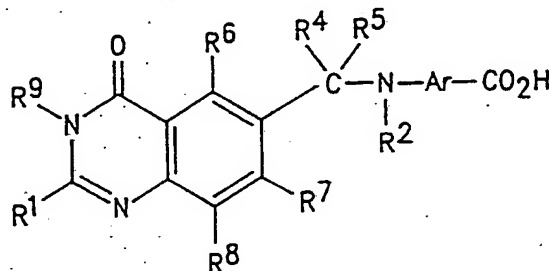methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,

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N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
05   N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
10   (prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
15   N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
20   ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
25   N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-(prop-
2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
30   methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-
2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,

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N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
05   N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-
glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
10   N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-ethyl-
amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid, and
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-
2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid;
as well as pharmaceutically acceptable salts, esters and amides
15   thereof.

A quinazoline of the invention may be prepared by any process
known to be applicable to the preparation of chemically-related
compounds.

The particularly preferred process for the manufacture of a
20   quinazoline of the invention comprises the reaction of an acid of
the formula:-

or a reactive derivative thereof,
with the terminal amino group of a dipeptide of the formula R^3-H
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Ar have the meanings
25   stated above, any mercapto, amino and alkylamino group in R^1, R^2,
R^3 and Ar and any carboxy group in R^1, R^2 and Ar is protected by a
conventional protecting group, and any hydroxy group in R^1, R^2, R^3
and Ar and any carboxy group in R^3 may be protected by a

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conventional protecting group or alternatively such a hydroxy or
carboxy group need not be protected; and wherein R^9 is hydrogen or
a protecting group, whereafter any undesired protecting group
including any protecting group R^9 is removed by conventional

05 means.

In this process, and the others described hereinafter, the
compound R^3-H, and also the quinazoline acid where appropriate,
conveniently has the stereochemical configuration at the asymmetric
carbon atoms therein which is desired in the final quinazoline of

10 formula (I). The reference to the protection of any amino group in
R^3 does not of course apply to the terminal amino group of the
dipeptide R^3-H.

A suitable reactive derivative of an acid of the formula given
above may be, for example, an acyl halide, for example an acyl

15 chloride formed by the reaction of the acid and an inorganic acid
chloride, for example thionyl chloride; a mixed anhydride, for
example an anhydride formed by the reaction of the acid and a
chloroformate such as isobutyl chloroformate; an active ester, for
example an ester formed by the reaction of the acid and a phenol

20 such as pentafluorophenol or an alcohol such as 1-hydroxybenzo-
triazole; the product of the reaction of the acid and a
carbodiimide, for example dicyclohexylcarbodiimide; or
particularly an acyl azide, for example an azide formed by the
reaction of the acid and an azide such as diphenylphosphoryl azide

25 or an acyl phosphonate, for example an acyl phosphonate formed by
the reaction of the acid and a phosphonate such as diethylcyano
phosphonate or (1H-1,2,3-benzotriazol-1-yloxy)-tris(pyrrolidino)-
phosphonium hexafluorophosphate.

A suitable protecting group for a hydroxy group is, for example,

30 an esterifying group, for example an acetyl or benzoyl group, which
may be removed by hydrolysis with a base, for example sodium
hydroxide, or provided that R^2 does not contain an alkenyl or
alkynyl group, the protecting group may be, for example, an
α-arylalkyl group, for example a benzyl group, which may be removed

35 by hydrogenation over a catalyst, for example palladium-on-charcoal.

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A suitable protecting group for an amino group may be, for example, an alkoxycarbonyl group, for example a <u>tert</u>-butyloxy-carbonyl group which may be removed by treatment with an organic acid, for example trifluoroacetic acid; or it may be, for example,
05   a benzyloxycarbonyl group or a trityl group which may be removed by catalytic hydrogenation.

A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine
10   or with hydrazine.

A suitable protecting group for a carboxy group may be an esterifying group, such as a <u>tert</u>-butyl group which may be removed by treatment with an organic acid, for example trifluoroacetic acid, thereby avoiding the possibility of racemization which can
15   arise with groups removable by base, although the use of a methyl group which may be removed by treatment with a base, for example sodium hydroxide, can be suitable in some cases.

A suitable alternative protecting group for a carboxy group is, for example, an allyl group which may be removed using catalytic
20   amounts of tetrakis triphenylphosphine palladium(0) in the presence of an excess of pyrrolidine.

A suitable protecting group for a mercapto group is, for example, an esterifying group, for example an acetyl group, which may be removed by hydrolysis with a base, for example sodium
25   hydroxide.

R^9 is preferably hydrogen rather than a protecting group but a suitable value for R^9 when it is a protecting group is, for example, a pivaloyloxymethyl group. Such a group may be removed by hydrolysis with a base, for example sodium hydroxide, but care
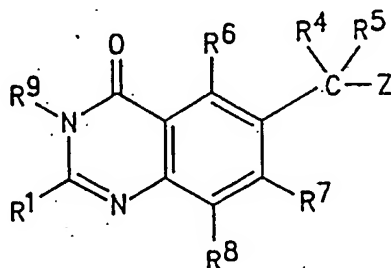30   should be taken to avoid racemization.

The protecting groups for the various carboxy groups in R^3 may be esterifying groups such as permit the product after removal of any undesired protecting group in R^1, R^2, R^3 and Ar and of any protecting group R^9 to fall within the definition of a quinazoline
35   of the invention. In such instance the esterified carboxy groups

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in R^3 may if desired be retained in the final product.
Alternatively a different protecting group may be used in R^3 which
will be removed.

05   The dipeptide compound of the formula R^3-H may be obtained by
any of the various general methods of peptide synthesis which are
described in the literature of peptide chemistry. Classical
methods involving reaction in solution or solid phase methods may
both be used. Preferably, however, the peptide R^3-H is prepared by
reaction of the appropriate two amino acids in solution, the amino
10   group of the acid providing the N-terminal residue of R^3-H and the
carboxy group of the acid providing the C-terminal residue of R^3-H
being protected, for example by protecting groups as described
hereinbefore, particularly suitable groups being a
benzyloxycarbonyl or trityl group and a <u>tert</u>-butyl or allyl
15   esterifying group, respectively. Although the amino protecting
group of the dipeptide will necessarily be removed before reaction
of R^3-H with the quinazoline carboxylic acid it may be convenient
to retain the carboxy protecting group which is already present in
the dipeptide.

20   The carboxylic acid used as starting material may be obtained
by the reaction of a compound of the formula:-

wherein R^1, R^4, R^5, R^6, R^7, R^8 and R^9 have the meanings stated
above, and Z is a displaceable group, with a compound of the
formula:

25                          $HNR^2-Ar-CO_2R^{10}$
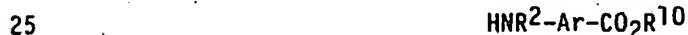
wherein R^2 and Ar have the meanings stated above and R^{10} is a
protecting group which can be removed to provide a carboxylic acid.

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Z may be, for example, a halogeno or sulphonyloxy group, for
example a chloro, bromo, methanesulphonyloxy or toluene-p-
sulphonyloxy group.

R^{10} may be, for example, a methyl or an ethyl group which may
05   be removed by hydrolysis with a base, for example sodium hydroxide
or R^{10} may be, for example, a <u>tert</u>-butyl group which may be removed
by cleavage with an organic acid, for example trifluoroacetic acid.

The protecting group for the carboxy group in R^{10} may be, for
example, an esterifying group which can be removed while the
10   protecting group for any mercapto, amino, carboxy and hydroxy group
in R^1, R^2 and Ar is retained.

An alternative procedure for the preparation of the carboxylic
acid starting material involves the use of carboxypeptidase G2
enzyme to remove the L-glutamic acid residue from a compound of
15   formula (I) but in which R^3 is instead such a residue.

A further preferred process for the manufacture of a
quinazoline of the invention, wherein R^1 is alkoxy, aryloxy or
alkoxy of up to 3 carbon atoms which bears one or more substituents
selected from hydroxy and alkoxy of up to 6 carbon atoms, comprises
20   the reaction of a compound of the formula:

with a compound of the formula:

$$HNR^2-Ar-COR^3$$
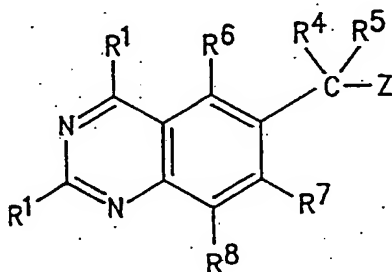
wherein R^1 has the last-mentioned meaning stated above;
wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, Ar and Z have the meanings
stated above, provided that any mercapto, amino, alkylamino and

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carboxy group in R^2, R^3 and Ar is protected by a conventional
protecting group, for example as stated above, and any hydroxy
group in R^1, R^2, R^3 and Ar may be protected by a conventional
protecting group, for example as stated above, or alternatively any
05   hydroxy group need not be protected;
whereafter any undesired protecting group is removed by
conventional means, for example as stated above, and the R^1 group
situated at the 4-position of the quinazoline ring is cleaved by
hydrolysis with a base, for example sodium hydroxide, to form a
10   quinazoline of the invention.

A further preferred process for the manufacture of a
quinazoline of the invention, wherein R^1 is mercapto or alkylthio
comprises the reaction of a quinazoline of the formula:-

$$R^9-N \begin{array}{c} O \\ \| \end{array} \quad R^6 \quad R^4 \quad R^5 \\ C-N-Ar-COR^3 \\ R^1 \qquad N \qquad R^7 \\ R^8 \\ R^2$$
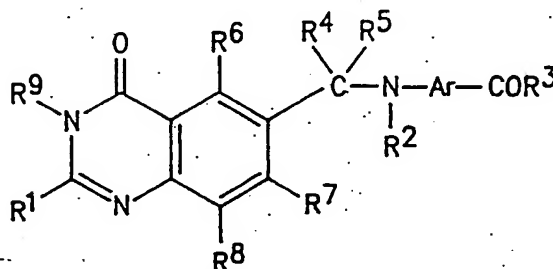
wherein R^1 is halogeno or halogenoalkyl and R^2, R^3, R^4, R^5, R^6, R^7,
15   R^8, R^9 and Ar have the meanings stated above, provided that any
mercapto, amino, alkylamino, carboxy and hydroxy group in R^2, R^3
and Ar may be protected by a conventional protecting group, for
example as stated above, or alternatively any amino, alkylamino,
carboxy and hydroxy group need not be protected;
20   with thiourea to provide a compound wherein R^1 is mercapto; or
with an alkyl thiol to provide a compound wherein R^1 is alkylthio,
arylthio whereafter any undesired protecting group including any
protecting group R^9 is removed by conventional means, for example
as stated above.

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A further preferred process for the manufacture of a
quinazoline of the invention wherein R^1 is alkylthio comprises the
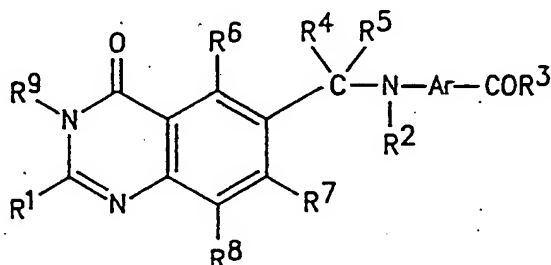reaction of a quinazoline of the formula:-

$$R^9-N \quad O \quad R^6 \quad \overset{R^4 \ R^5}{C}-N-Ar-COR^3 \quad R^1 \quad N \quad R^7 \quad R^8 \quad R^2$$

wherein R^1 is mercapto and R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and Ar
05   have the meanings stated above, provided that any mercapto, amino,
alkylamino, carboxy and hydroxy group in R^2, R^3 and Ar may be
protected by a conventional protecting group, for example as stated
above, or alternatively any amino, alkylamino, carboxy and hydroxy
group need not be protected; with a base, for example ammonium
10   hydroxide, followed by alkylation of the resultant thiolate salt
with an alkyl halide, for example methyl iodide; whereafter any
undesired protecting group including any protecting group R^9 is
removed by conventional means, for example as stated above.

An alternative process for the manufacture of a quinazoline of
15   the invention comprises the reaction of a compound of the formula:-

$$R^9-N \quad O \quad R^6 \quad \overset{R^4 \ R^5}{C}-Z \quad R^1 \quad N \quad R^7 \quad R^8$$

with a compound of the formula:-

$$HNR^2-Ar-COR^3$$
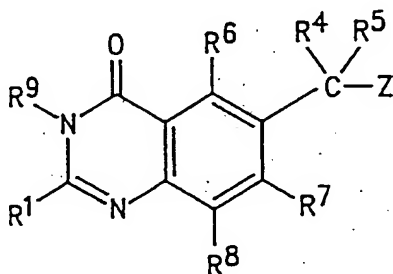
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and within these compounds R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and
Ar have the meanings stated above, provided that when there is a
hydroxy group in R^1, R^3 or Ar, when there is a hydroxyalkyl group
in R^1 or R^2 when there is a hydroxyalkoxy group in R^1, when there
05 is an amino group in R^1, R^3 or Ar, when there is an aminoalkyl
group in R^2, when there is an alkylaminoalkyl group in R^2, when
there is a carboxy or carboxyalkyl group in R^2 or R^3 or when there
is a mercapto or mercaptoalkyl group in R^1, R^2 or R^3 any amino,
carboxy and mercapto group is protected by a conventional
10 protecting group, for example as stated above, and any hydroxy
group may be protected by a conventional protecting group, for
example as stated above, or alternatively any hydroxy group need
not be protected; Z is a displaceable group; whereafter any
undesired protecting group including any protecting group R^9 is
15 removed by conventional means, for example as stated above.

When a pharmaceutically acceptable salt of a novel compound of
the formula (I) is required, it may be obtained, for example, by
reaction of said compound with a suitable acid or base using a
conventional procedure. When a pharmaceutically acceptable salt of
20 a novel compound of the formula (I) is required, it may be obtained,
for example, by reaction of said compound with a suitable acid or
alcohol using a conventional procedure. When a pharmaceutically
acceptable salt of a novel compound of the formula (I) is required,
it may be obtained, for example, by reaction of said compound or a
25 suitable derivative thereof such as the acid chloride with ammonia
or a suitable amine. When an optically active form of a compound
of the formula (I) is required, it may be obtained by carrying out
one of the aforesaid processes using an optically active starting
material, or by resolution of a racemic form of said compound using
30 a conventional procedure.

As stated above quinazolines are believed to function as
anti-cancer agents at least in part due to their ability to inhibit
the enzyme thymidylate synthase. This anti-cancer activity may be
assessed, for example, using one or more of the procedures set out
35 below:-

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(a) An _in vitro_ assay which determines the ability of a test
compound to inhibit the enzyme thymidylate synthase. Thymidylate
synthase may be obtained in partially purified form from L1210
mouse leukaemia cells and utilised in the assay using the
05   procedures described by Jackman _et al_ (Cancer Res., 1986, _46_, 2810);
(b) An assay which determines the ability of a test compound to
inhibit the growth of the leukaemia cell line L1210 in cell
culture. The test may be similar to that described in UK Patent
Specification No. 2065653B; and
10   (c) An assay which determines the ability of a test compound to
inhibit the growth of the human breast cancer cell line MCF-7 in
cell culture. The test may be similar to that described by
Lippman _et al_ (Cancer Res., 1976, _36_, 4595).

Although the pharmacological properties of quinazolines of the
15   invention vary with structural change, in general quinazolines of
the invention possess thymidylate synthase inhibitory properties at
the following concentrations:- IC_{50} in the range, for
example, 0.001-10 or 20 μM; or quinazolines of the invention
possess L1210 cell-line inhibitory properties at the following
20   concentrations:- IC_{50} in the range, for example, 0.001-50 or
100 μM.

In general those quinazolines of the invention which are
especially preferred possess thymidylate synthase inhibitory
properties at the following concentration:- IC_{50} of less
25   than 1 μM; or they possess L1210 cell-line inhibitory properties
at the following concentration:- IC_{50} of less than 10 μM.

As regards the inhibition of the MCF-7 cancer cell line, in
general quinazolines of the invention possess inhibitory properties
at the following concentrations:- IC_{50} in the range, for example,
30   0.1-50 or -100 μM. Especially preferred quinazolines possess MCF-7
cell line inhibitory properties at the following concentration:-
IC_{50} of less than 5 μM.

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Thus, by way of example, the quinazoline N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid, has an IC_{50} of 0.0095 µM against thymidylate synthetase, an IC_{50} of 0.24 µM against the

05   L1210 cell line, an IC_{50} of 0.3 µM against the MCF-7 cell line.

In vivo tests in mice at a dosage of 100 mg/kg with various compounds according to the invention have shown a substantial lack of cleavage of the central amide linkage of the dipeptide as assessed by measurement of the amount of the cleavage product as a

10   percentage of the total of parent compound and cleavage product present in the liver or plasma of a mouse sacrificed 1 hour after intraperitoneal administration of the dipeptide, i.e. cleavage was within the limit of experimental detection which is about 5%. Although a minor degree of cleavage of this amide linkage of the

15   quinazoline is acceptable when it is used in practice, a level of cleavage on administration in vivo of less than 10% is preferred, with no more than about 5% being desirable, especially 2% or 1% or less.

A quinazoline of the invention may be administered to a

20   warm-blooded animal, including a human, in the form of a pharmaceutical composition which comprises the quinazoline in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, as a tablet or capsule, or, especially, for

25   parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), as a sterile solution, suspension or emulsion, or for topical administration, as an ointment or cream, or for rectal administration as a suppository.

The composition may contain, in addition to the quinazoline of

30   the invention, one or more other anti-cancer substances selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; other antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea;

35   intercalating antibiotics, for example adriamycin and bleomycin;

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enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide and biological response modifiers, for example interferon.

In general the compositions may be prepared in a conventional
05   manner using conventional excipients.

The quinazoline will normally be administered to a warm-blooded animal at a dose within the range 50-25000 mg per square metre body area of the animal, i.e. approximately 1-500 mg/kg. Where desired, however, dosages outside this range may be employed and, in
10   particular, where the preferred mode of administration involving subcutaneous infusion is used then the does range may be increased to 1-1000 mg/kg. Preferably a daily dose in the range 10-150 mg/kg is employed, particularly 30-80 mg/kg.

Accordingly the present invention also includes a method for
15   aiding regression and palliation of cancer in a patient, particularly a warm-blooded animal such as man, in need of such treatment, which comprises administering to said patient an effective amount of a quinazoline as defined hereinbefore. The invention also provides the use of such a quinazoline in the
20   manufacture of a novel medicament for use in the treatment of cancer.

Quinazolines of the present invention are of interest for a wide range of anti-tumour activities, particularly in the human, including the treatment of breast, ovarian and liver cancer. In
25   addition they are of interest in the context of the treatment of a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas.

In view of the activity shown by antimetabolites such as aminopterin and methotrexate, which is discussed hereinbefore, the
30   quinazolines of the present invention are also of interest for use in the treament of other conditions, for example allergic conditions such as psoriasis. In using a quinazoline of the invention for such a purpose the compound will normally be administered at a dose within the range 50-25000 mg per square
35   metre body area of the animal, i.e. approximately 1-500 mg/kg.

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Where desired, however, dosages outside this range may be employed.
In general, for the treatment of an allergic condition such as
psoriasis topical administration of a quinazoline of the invention
is preferred. Thus, for example, for topical administration a
05 daily dose in the range, for example, of 10-150 mg/kg may be used,
particularly 30-80 mg/kg.

Compositions containing the quinazolines may be formulated in
unit dosage form, i.e. in the form of discrete portions each
comprising a unit dose, or a multiple or sub-multiple of a unit
10 dose, for example an amount of the quinazoline in the range
of 1-250 or 500 mg.

The invention is illustrated by the following Examples.

The structures of all compounds of the invention were confirmed
by proton magnetic resonance and mass spectroscopy and by elemental
15 analysis. Proton magnetic resonance and mass spectra were
determined using a Bruker WM250 spectrometer operating at a field
strength of 250 MHz. Chemical shifts are reported in parts per
million downfield from tetramethylsilane as an internal standard
(δ scale) and peak multiplicities are shown thus: s, singlet;
20 d, doublet; d of d's, doublet of doublets; t, triplet;
m, multiplet, the attribution believed to be appropriate for each
signal also being indicated. Mass spectra were obtained using a
VG analytical ZAB SE spectrometer with fast-atom bombardment
ionization (FAB) or a Finnigan TSQ 700 spectrometer with
25 electrospray ionization (ESI) or chemical ionization (CI). Where
appropriate, either positive ion data or negative ion data were
collected.

Column chromatography was performed using Merck Art 15111
silica gel. Petroleum ether refers to the fraction of boiling
30 point 60-80°C.

Intermediates for the preparation of compounds according to the
invention containing other groups R^1, R^2, R^4 to R^8 and Ar are
described in UK patents 2 065 653, 2 175 903, 2 188 319 and
2 202 847 and in UK patent applications 2 217 709, 2 227 016 and
35 2 244 708, and in the equivalents thereof filed in other countries.

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EXAMPLES

Example 1: N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-
glutamic acid.

05   (1) Tri-tert-butyl-L-γ-glutamyl-N-methyl-L-glutamate.

N-Methyl-L-glutamic acid (3.2 g) was added to water (50 ml) and
the pH of the solution adjusted to 9 with solid sodium bicarbonate.
The solution was cooled to 0°C and stirred vigorously, while benzyl
chloroformate (9 ml) was added dropwise over 20 min. The mixture

10   was stirred for a further 2 h at 0°C and an additional 2 h at room
temperature, then extracted with diethyl ether (2 x 100 ml).
The aqueous solution was then acidified to pH 3 with 5N HCl and the
product isolated by extraction with ethyl acetate (2 x 100 ml).
The pooled organic extracts were dried over anhydrous sodium

15   sulphate and the solvent concentrated in vacuo to give a yellow
oil, which crystallised on standing. Recrystallisation from water
afforded N-(benzyloxycarbonyl)-N-methyl-L-glutamic acid (2.26 g),
m.p. 97-98°C.
NMR Spectrum: (CD$_3$SOCD$_3$, 67°C) 1.94, 2.14 (2 x m, 2H, β-CH$_2$),

20   2.22 (t, 2H, J = 6.27 Hz, γ-CH$_2$), 2.79 (s, 3H, N-CH$_3$), 4.53 (dd,
J = 5.0, 10.4 Hz, 1H, α-CH), 5.08 (s, 2H, ArCH$_2$), 7.33 (m, 5H, ArH).
Mass Spectrum: (CI) m/e 296 (M+H)$^+$.
Elemental Analysis: Found C, 56.67; H, 5.78; N, 4.72%.
C$_{14}$H$_{17}$NO$_6$ requires C, 56.95; H, 5.80; N, 4.74%.

25   N-(Benzyloxycarbonyl)-N-methyl-L-glutamic acid (1.85 g) was
suspended in dichloromethane (52 ml) in a pressure bottle and to
this was added concentrated sulphuric acid (0.28 ml). The mixture
was cooled to -20°C and liquid isobutylene (25 ml) added. The
stoppered reaction vessel was shaken vigorously at room temperature

30   for 28 hours, then cooled and a saturated solution of sodium
bicarbonate (100 ml) and ethyl acetate (200 ml) were added. The
organic layer was separated and washed with saturated sodium
bicarbonate solution (2 x 160 ml) and water (100 ml), then dried
over anhydrous sodium sulphate, filtered and concentrated in vacuo.

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The residue was purified by chromatography on a silica gel column using 10% ethyl acetate in dichloromethane as eluant. There was thus obtained di-<u>tert</u>-butyl <u>N</u>-(benzyloxycarbonyl)-<u>N</u>-methyl-L-glutamic acid (1.8 g) as an oil.

05   NMR Spectrum: (CD_3SOCD_3, 67°C) 1.37, 1.38 (2 x s, 18H, $C(CH_3)_3$), 1.90, 2.07 (2 x m, 2H, β-CH_2), 2.20 (m, 2H, γ-CH_2), 2.79 (s, 3H, N-CH_3), 4.44 (dd, J = 5.3, 10.2 Hz, 1H, α-CH), 5.11 (m, 2H, ArCH_2), 7.33 (m, 5H, ArH).

Mass Spectrum: (CI) m/e 408 (M+H)$^+$.

10   Elemental Analysis: Found C, 64.74; H, 8.15; N, 3.40%.
$C_{22}H_{33}NO_6$ requires C, 64.84; H, 8.16; N, 3.44%.

A solution of di-<u>tert</u> butyl <u>N</u>-(benzyloxycarbonyl)-<u>N</u>-methyl-L-glutamic acid (1.6 g) in ethyl acetate containing 10% Pd/C (0.22 g) was stirred under hydrogen for 2.5 hours. The catalyst

15   was removed by filtration and the filtrate concentrated to dryness <u>in vacuo</u>, yielding di-<u>tert</u>-butyl <u>N</u>-methyl-L-glutamic acid (1.14 g) as an oil.

NMR Spectrum: (CD_3SOCD_3) 1.39, 1.42 (2 x s, 18H, C ($CH_3)_3$), 1.67 (m, 2H, β-CH_2), 2.19 (s, 3H, N-CH_3), 2.23 (m, 2H, γ-CH_2), 2.91

20   (dd, J = 6.1, 7.8 Hz, 1H, α-CH).

Mass spectrum: (CI) m/e 274 (M+H)$^+$.

To a stirred solution of α-<u>tert</u>-butyl-<u>N</u>-benzyloxycarbonyl-L-glutamate (Org. Prep. Proc. Int., 1985, <u>17</u>, 416; 1.31 g) and <u>N</u>-methylmorpholine (0.37 g) in dry tetrahydrofuran (5 ml)

25   cooled to -20°C was added isobutyl chloroformate (0.50 g). After 10 minutes a solution of di-<u>tert</u>-butyl <u>N</u>-methyl-L-glutamic acid (1.003 g) in tetrahydrofuran (5 ml) was added. Stirring was continued for 10 minutes at -20°C, and then at laboratory temperature for 4 hours. <u>N</u>-methylmorpholine hydrochloride was

30   filtered off and the filtrate concentrated <u>in vacuo</u>. The residue was purified by chromatography on a silica gel column using a gradient of ethyl acetate in dichloromethane (5-30% v/v) as eluant. The product was triturated in diethyl ether and the white solid isolated by filtration, washed with petrol and dried <u>in vacuo</u>.

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There was thus obtained tri-tert-butyl N-methyl-[N-(benzyloxy
carbonyl)-L-γ-glutamyl]- L-glutamate (1.62 g), m.p. 92-93°C.
NMR Spectrum: (CD₃SOCD₃) 1.32, 1.37, 1.38 (3 x s, 27H, C(CH₃)₃),
1.86, 2.03 (2 x m, 4H, β-CH₂), 2.12, 2.38 (2 x m, 4H, γ-CH₂), 2.60,
05   2.79 (2 x s, 3H, N-CH₃), 3.94 (m, 1H, glu α-CH), 4.49, 4.76 (2 x dd,
J = 4.8, 10.8 Hz, 1H, N-Me glu α-CH), 5.03 (m, 2H, ArCH₂),
7.35 (s, 5H, ArH), 7.64 (t, J = 7.7 Hz, 1H, NH).
Mass Spectrum: (CI) m/e 593 (M+H)⁺.
Elemental Analysis: Found C, 62.84; H, 8.16; N, 4.69%.
10   C₃₁H₄₈N₂O₉ requires C, 62.82; H, 8.16; N, 4.73%.

        A solution of tri-tert-butyl N-methyl-[N-(benzyloxycarbonyl)-
L-γ-glutamyl]-L-glutamate (0.80 g) in ethyl acetate containing
10% Pd/C (0.11 g) was stirred under hydrogen for 3 hours. The
catalyst was removed by filtration and the filtrate concentrated
15   in vacuo, yielding tri-tert-butyl-L-γ-glutamyl-N-methyl-L-glutamate
(0.61 g) as an oil.
NMR Spectrum: (CD₃SOCD₃) 1.38, 1.39, 1.41, 1.42 (4 x s, 27H,
C(CH₃)₃), 1.79, 2.05 (2 x m, 4H, β-CH₂), 2.12, 2.39 (2 x m, 4H,
γ-CH₂), 2.60, 2.84 (2 x s, 3H, N-CH₃), 3.18 (dd, J = 8.3, 4.9 Hz,
20   1H, CHNH₂), 4.53, 4.78 (2 x dd, J = 10.5, 4.6 Hz, 1H, N-Me glu
α-CH).
Mass Spectrum: (CI) m/e 459 (M+H)⁺.

(2) N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoic acid
25   A mixture of tert-butyl p-aminobenzoate (Synth. Commun., 1984,
14, 921; 10.5 g), propargyl bromide (7.3 ml of an 80% solution in
toluene), potassium carbonate (7.5 g) and N,N-dimethylacetamide
(85 ml) was heated to 50°C for 24 hours, cooled, filtered and
evaporated. The residue was purified by chromatography on a silica
30   gel column using a 6:1 v/v mixture of hexane and ethyl acetate as
eluant.

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There was thus obtained tri-tert-butyl N-methyl-[N-(benzyloxy
carbonyl)-L-γ-glutamyl]- L-glutamate (1.62 g), m.p. 92-93°C.
NMR Spectrum: (CD_3SOCD_3) 1.32, 1.37, 1.38 (3 x s, 27H, $C(CH_3)_3$),
1.86, 2.03 (2 x m, 4H, β-CH_2), 2.12, 2.38 (2 x m, 4H, γ-CH_2), 2.60,
05   2.79 (2 x s, 3H, N-CH_3), 3.94 (m, 1H, glu α-CH), 4.49, 4.76 (2 x dd,
J = 4.8, 10.8 Hz, 1H, N-Me glu α-CH), 5.03 (m, 2H, $ArCH_2$),
7.35 (s, 5H, ArH), 7.64 (t, J = 7.7 Hz, 1H, NH).
Mass Spectrum: (CI) m/e 593 $(M+H)^+$.
Elemental Analysis: Found C, 62.84; H, 8.16; N, 4.69%.
10    $C_{31}H_{48}N_2O_9$ requires C, 62.82; H, 8.16; N, 4.73%.

        A solution of tri-tert-butyl N-methyl-[N-(benzyloxycarbonyl)-
L-γ-glutamyl]-L-glutamate (0.80 g) in ethyl acetate containing
10% Pd/C (0.11 g) was stirred under hydrogen for 3 hours. The
catalyst was removed by filtration and the filtrate concentrated
15   in vacuo, yielding tri-tert-butyl-L-γ-glutamyl-N-methyl-L-glutamate
(0.61 g) as an oil.
NMR Spectrum: (CD_3SOCD_3) 1.38, 1.39, 1.41, 1.42 (4 x s, 27H,
$C(CH_3)_3$), 1.79, 2.05 (2 x m, 4H, β-CH_2), 2.12, 2.39 (2 x m, 4H,
γ-CH_2), 2.60, 2.84 (2 x s, 3H, N-CH_3), 3.18 (dd, J = 8.3, 4.9 Hz,
20   1H, $CHNH_2$), 4.53, 4.78 (2 x dd, J = 10.5, 4.6 Hz, 1H, N-Me glu
α-CH).
Mass Spectrum: (CI) m/e 459 $(M+H)^+$.

(2) N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoic acid
25   A mixture of tert-butyl p-aminobenzoate (Synth. Commun., 1984,
14, 921; 10.5 g), propargyl bromide (7.3 ml of an 80% solution in
toluene), potassium carbonate (7.5 g) and N,N-dimethylacetamide
(85 ml) was heated to 50°C for 24 hours, cooled, filtered and
evaporated. The residue was purified by chromatography on a silica
30   gel column using a 6:1 v/v mixture of hexane and ethyl acetate as
eluant.

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A mixture of the product (7.3 g); 6-bromomethyl-3,4-dihydro-2-methylquinazolin-4-one (8g; prepared as described in Example 3 of UK Patent 2 188 319B), calcium carbonate (3.2 g) and dimethylformamide (100 ml) was stirred at laboratory temperature for 65 hours, filtered and evaporated. The residue was purified by chromatography on a silica gel column using ethyl acetate as eluant.

The mixture of the product (2.5 g) and trifluoroacetic acid (25 ml) was stirred at laboratory temperature for 10 minutes and evaporated to give the p-aminobenzoic acid as its trifluoroacetic acid salt (2.5 g).

(3) N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid.

A mixture of N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid salt (0.461 g) and tri-tert-butyl-L-γ-glutamyl-N-methyl-L-glutamate (0.60 g) was dissolved in dry dimethylformamide (15 ml) at 0°C and to this solution was added diethyl cyanophosphonate (0.359 g) and then triethylamine (0.222 g) under a nitrogen atmosphere. The solution was stirred at 0°C and in the dark for 20 minutes and then at laboratory temperature for 2 hours, then diluted with ethyl acetate (100 ml) and water (100 ml). The water layer was separated and extracted with ethyl acetate (2 x 100 ml). The combined ethyl acetate extracts were washed with 10% aqueous citric acid (2 x 50 ml), saturated sodium bicarbonate (100 ml) and dilute aqueous sodium chloride (100 ml), then dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was purified by chromatography on a silica gel column using ethyl acetate as eluant. The product was precipitated from dichloromethane/petroleum ether and there was thus obtained tri-tert-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamate (0.56 g), m.p. 110-113°C.

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NMR Spectrum: (CD_3SOCD_3) 1.32, 1.33, 1.35, 1.36, 1.39 (5 x s, 27H, $C(CH_3)_3$), 1.86 (m, 4H, β-CH_2), 2.32 (s, 3H, quinazoline 2-CH_3), 2.15, 2.44 (2 x m, 4H, γ-CH_2), 2.61, 2.80 (2 x s, 3H, N-CH_3), 3.23 (s, 1H, C≡CH), 4.29 (m, 3H, CH_2C≡C, glu α-CH), 4.48,

05   4.77 (2 x m, 3H, quinazoline 6-CH_2, N-Me glu α-CH), 6.82 (d, J = 8.7 Hz, 2H, 3',5'-ArH), 7.54 (d, J = 8.4 Hz, 1H, quinazoline 8-H), 7.71 (t, J = 8.6 Hz, 3H, quinazoline 7-H, 2',6'-ArH), 7.96 (s, 1H, quinazoline 5-H), 8.28 (t, 1H, glu NH), 12.19 (s, 1H, lactam NH).

10   Mass Spectrum: (positive ion FAB) m/e 810 (M+Na)$^+$.
Elemental Analysis: Found C, 64.75; H, 7.19; N, 8.73%.
$C_{43}H_{57}N_5O_9$.0.5H_2O requires C, 64.81; H, 7.33; N, 8.79%.

A mixture of tri-_tert_-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-benzoyl-L-γ-

15   glutamyl-N-methyl-L-glutamate (0.167 g) and trifluoroacetic acid (10 ml) was stirred at laboratory temperature for 1 hour in the dark. The solution was then concentrated _in vacuo_ and the residue triturated with diethyl ether (30 ml). The white solid was isolated by filtration, washed with diethyl ether (4 x 10 ml) and

20   dried _in vacuo_. There was thus obtained N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid, trifluoroacetic acid salt (0.152 g), m.p. 205°C decomp.
NMR Spectrum: (CD_3SOCD_3) 1.80-2.14 (m, 4H, β-CH_2), 2.42 (s, 3H,

25   quinazoline 2-CH_3), 2.14, 2.45 (2 x m, 4H, γ-CH_2), 2.65, 2.81 (2 x s, 3H, N-CH_3), 3.24 (s, 1H, C≡CH), 4.35 (s, 3H, CH_2C≡C, glu α-CH), 4.81 (s, 2H, quinazoline 6-CH_2), 4.58, 4.91 (dd, J = 11.0, 4.5 Hz, 1H, N-Me glu α-CH), 6.83 (d, J = 8.7 Hz, 2H, 3',5'-ArH), 7.59 (d, J = 8.4 Hz, 1H, quinazoline 8-H),

30   7.75 (m, 3H, 2',6'-ArH, quinazoline 7-H), 8.00 (s, 1H, quinazoline 5-H); 8.32 (d, J = 7.3 Hz, 1H, glu NH).
Mass Spectrum: (positive ion FAB) m/e 642 (M+Na)$^+$.
Elemental Analysis: Found C, 52.93; H, 5.18; N, 8.41; F, 7.65%.
$C_{31}H_{33}N_5O_9$·1.1CF_3COOH·0.5Et_2O·1H_2O requires C, 52.84; H, 5.18;

35   N, 8.75; F, 7.83%.

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Example 2: N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]-benzoyl-L-γ-glutamyl-N-methylglycine

(1) Di-tert-butyl-L-γ-glutamyl-N-methylglycine.

    N-methylglycine (7.0 g) was added to water (50 ml) and the pH
05   of the solution adjusted to 9 with solid sodium bicarbonate. The
solution was cooled to 0°C and stirred vigorously, while benzyl
chloroformate (19 ml) was added dropwise over 20 minutes. The
mixture was stirred for a further 2 hours at 0°C and an additional
2 hours at room temperature, then extracted with diethyl ether
10   (2 x 130 ml). The aqueous solution was then acidified to pH 3 with
5N HCl and the product isolated by extraction with ethyl acetate
(2 x 130 ml). The combined organic extracts were dried over
anhydrous sodium sulphate and the solution concentrated in vacuo to
give N-(benzyloxycarbonyl)-N-methylglycine as a pale yellow oil
15   (16.2 g).

NMR Spectrum: (CD$_3$SOCD$_3$, 72°C) 2.91 (s, 3H, N-CH$_3$), 3.94 (s, 2H,
CH$_2$CO$_2$H), 5.07 (s, 2H, ArCH$_2$), 7.33 (s, 5H, ArH).

Mass Spectrum: (ESI) m/e 223 (M$^+$).

    To a stirred solution of N-(benzyloxycarbonyl)-N-methylglycine
20   (7.86 g) and tertiary butyl alcohol (4.68 ml) in chloroform (30 ml)
cooled in an ice-water bath was added a solution of
dicyclohexylcarbodiimide (8.0 g) in chloroform (30 ml), and then
4-dimethylaminopyridine (0.04 g) as catalyst. Stirring was
continued at 0°C for 2 hours, then the mixture was kept at 4°C
25   overnight. Dicyclohexylurea was removed by filtration and the
solvent concentrated in vacuo. The residue was dissolved in ethyl
acetate (110 ml) and acetic acid (1.10 ml) was added. The solution
was stored at 4°C for 2 hours. After filtration, the ethyl acetate
was washed with 5% aqueous sodium bicarbonate solution (2 x 70 ml),
30   water (3 x 80 ml) and dried over anhydrous magnesium sulphate. The
solution was concentrated in vacuo and the residue purified by
chromatography on a silica gel column using 30% ethyl acetate in
petrol as eluant. There was thus obtained tert-butyl-N-(benzyloxy-
carbonyl)-N-methylglycine (3.6 g) as an oil.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.36, 1.41 (2 x s, 9H, C(CH$_3$)$_3$), 2.88,

2.91 (2 x s, 3H, N-CH$_3$), 3.91, 3.94 (2 x s, 2H, CH$_2$COOH), 5.05,

5.10 (2 x s, 2H, ArCH$_2$), 7.31, 7.36 (2 x m, 5H, ArH).

Mass Spectrum: (ESI) m/e 279 (M$^+$).

05   Elemental Analysis: Found C, 64.27; H, 7.62; N, 5.03%.

C$_{15}$H$_{21}$NO$_4$ requires C, 64.50; H, 7.58; N, 5.01%.

A solution of tert-butyl-N-(benzyloxycarbonyl)-N-methylglycine

(1.60 g) in ethyl acetate containing 10% Pd/C (0.23 g) was stirred

under hydrogen for 2.5 hours. The catalyst was removed by

10   filtration and the filtrate concentrated in vacuo, yielding

tert-butyl-N-methylglycine (0.71 g) as an oil.

NMR Spectrum: (CD$_3$SOCD$_3$) 1.41 (s, 9H, C(CH$_3$)$_3$), 2.25 (s, 3H,

N-CH$_3$), 3.13 (s, 2H, CH$_2$).

Mass Spectrum: (CI) m/e 146 (M+H)$^+$.

15   To a stirred solution of α-tert-butyl-N-benzyloxycarbonyl-L-

glutamate (1.63 g) and N-methylmorpholine (0.487 g) in dry

tetrahydrofuran (8 ml) cooled to -20°C was added isobutyl

chloroformate (0.657 g). After 10 minutes a solution of

tert-butyl-N-methylglycine (0.70 g) in tetrahydrofuran (8 ml) was

20   added. Stirring was continued for 10 minutes at -20°C, and then at

laboratory temperature for 4 hours. N-methylmorpholine

hydrochloride was filtered off and the filtrate concentrated

in vacuo. The residue was purified by chromatography on a silica

gel column using 5% ethyl acetate in dichloromethane as eluant,

25   affording di-tert-butyl-N-methyl-[N-(benzyloxycarbonyl)-L-γ-

glutamyl]glycine as a yellow oil (1.73 g).

NMR Spectrum: (CD$_3$SOCD$_3$) 1.32, 1.38, 1.39, 1.41 (4 x s, 18H,

C(CH$_3$)$_3$), 1.77, 1.87 (2 x m, 2H, β-CH$_2$), 2.24, 2.38 (2 x m, 2H,

γ-CH$_2$), 2.79, 2.95 (2 x s, 3H, N-CH$_3$), 3.93(m) and 4.08(s)

30   (3H, CH$_2$CO$_2$Bu^t, α-CH), 5.03 (m, 2H, ArCH$_2$), 7.36 (m, 5H, ArH),

7.64 (t, 1H, NH).

Mass Spectrum: (CI) m/e 465 (M+H)$^+$.

Elemental Analysis: Found C, 61.56; H, 7.81; N, 5.97%.

C$_{24}$H$_{36}$N$_2$O$_7$·0.5H$_2$O requires C, 61.45; H, 7.84; N, 5.97%.

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A solution of di-tert-butyl-N-methyl-[N-(benzyloxycarbonyl)-
L-γ-glutamyl]glycine (0.80 g) in ethyl acetate containing 10% Pd/C
(0.150 g) was stirred under hydrogen for 6 hours. The catalyst was
removed by filtration and the filtrate concentrated in vacuo,
05   yielding di-tert-butyl-L-γ-glutamyl-N-methylglycine (0.53 g) as a
yellow oil.
NMR Spectrum: (CD$_3$SOCD$_3$) 1.40, 1.41, 1.43 (3 x s, 18H, C(CH$_3$)$_3$),
1.59, 1.77 (2 x m, 2H, β-CH$_2$), 2.24, 2.40 (2 x m, 2H, γ-CH$_2$), 2.79,
2.99 (2 x s, 3H, N-CH$_3$), 3.17 (m, 1H, α-CH), 4.02(s) and 4.10(d)
10   (2H, CH$_2$CO$_2$Bu^t).
Mass Spectrum: (ESI) m/e 331 (M+H)$^+$.

(2) N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methylglycine.
A mixture of N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-
15   6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid
salt (0.553 g) and di-tert-butyl-L-γ-glutamyl-N-methylglycine
(0.53 g) was dissolved in dry dimethylformamide (15 ml) at 0°C and
to this solution was added diethyl cyanophosphonate (0.359 g) and
then triethylamine (0.222 g) under a nitrogen atmosphere. The
20   solution was stirred at 0°C and in the dark for 20 minutes and then
at laboratory temperature for 3 hours, then diluted with ethyl
acetate (100 ml) and water (100 ml). The water layer was separated
and extracted with ethyl acetate (2 x 100 ml). The combined ethyl
acetate extracts were washed with 10% aqueous citric acid (2 x 50
25   ml), saturated sodium bicarbonate (100 ml) and dilute aqueous
sodium chloride (100 ml), then dried over sodium sulphate, filtered
and concentrated in vacuo. The residue was purified by
chromatography on a silica gel column using ethyl acetate as
eluant. The product was precipitated from cold
30   dichloromethane/diethyl ether and there was thus obtained
di-tert-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methylglycine
(0.22 g), m.p. 104-108°C.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.30, 1.39 (2 x s, 18H, C(CH$_3$)$_3$),
2.33 (s, 3H, quinazoline 2-CH$_3$), 1.96 (m, 2H, β-CH$_2$), 2.26,
2.45 (2 x m, 2H, γ-CH$_2$), 2.79, 2.95 (2 x s, 3H, N-CH$_3$),
3.23 (s, 1H, C≡CH), 3.95(d) and 4.06(s) (2H, CH$_2$CO$_2$),
05   4.25 (m, 1H, α-CH), 4.33 (s, 2H, CH$_2$C≡C), 4.77 (s, 2H,
quinazoline 6-CH$_2$), 6.81 (m, 2H, 3',5'-ArH), 7.54 (d, J = 8.3 Hz,
1H, quinazoline 8-H), 7.74 (m, 3H, quinazoline 7-H, 2',6'-ArH),
7.96 (s, 1H, quinazoline 5-H), 8.28 (t, 1H, NH), 12.19 (s, 1H,
lactam NH).
10   Mass Spectrum: (positive ion FAB) m/e 682 (M+Na)$^+$.
Elemental Analysis: Found C, 65.12; H, 6.86; N, 10.50%.
C$_{36}$H$_{45}$N$_5$O$_7$·0.25H$_2$O requires C, 65.09; H, 6.90; N, 10.54%.

A mixture of di-tert-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-
oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-
15   glutamyl-N-methylglycine (0.074 g) and trifluoroacetic acid (5 ml)
was stirred at laboratory temperature for 1 hour in the dark. The
solution was then concentrated in vacuo and the residue triturated
with diethyl ether (20 ml). The white solid was isolated by
filtration, washed with diethyl ether (4 x 10 ml) and dried
20   in vacuo. There was thus obtained N-p-[N-(3,4-dihydro-2-
methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-
L-γ-glutamyl-N-methylglycine, trifluoroacetate salt (0.60 g),
m.p. 140°C decomp.
NMR Spectrum: (CD$_3$SOCD$_3$) 2.01 (m, 2H, β-CH$_2$), 2.33,
25   2.42 (2 x m, 2H, γ-CH$_2$), 2.42 (s, 3H, quinazoline 2-CH$_3$), 2.81,
2.97 (2 x s, 3H, N-CH$_3$), 3.24 (s, 1H, C≡CH), 3.98 (d, J = 8.0 Hz)
and 4.10(s) (2H, CH$_2$CO$_2$), 4.36 (m, 3H, CH$_2$C≡C, α-CH), 4.81 (s, 2H,
quinazoline 6-CH$_2$), 6.84 (d, J = 8.3 Hz, 2H, 3',5'-ArH),
7.59 (d, J = 8.5 Hz, 1H, quinazoline 8-H), 7.76 (m, 3H, quinazoline
30   7-H, 2',6'-ArH), 8.01 (s, 1H, quinazoline 5-H), 8.33 (t, 1H, NH).
Mass Spectrum: (positive ion FAB) m/e 570 (M+Na)$^+$.
Elemental Analysis: C, 53.98; H, 5.63; N, 9.02; F, 8.15%.
C$_{28}$H$_{29}$N$_5$O$_7$·1.1CF$_3$COOH·0.8H$_2$O.0·8Et$_2$O requires C, 53.72; H, 5.35;
N, 9.38; F, 8.39%.

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Example 3: N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-L-proline.

(1) Di-tert-butyl-L-γ-glutamyl-L-proline.

To a stirred solution of α-tert-butyl-N-benzyloxycarbonyl-L-
05   glutamate (3.15 g) and N-methylmorpholine (0.909 g) in dry
tetrahydrofuran (10 ml) cooled to -20°C was added isobutyl
chloroformate (1.22 g). After 10 minutes a solution of
tert-butyl-L-proline (1.54 g) in tetrahydrofuran (10 ml) was
added. Stirring was continued for 10 minutes at -20°C, and then at
10   laboratory temperature for 4 hours. N-methylmorpholine
hydrochloride was filtered off and the filtrate concentrated
in vacuo. The residue was purified by chromatography on a silica
gel column using a gradient of 10% to 30% ethyl acetate in
dichloromethane as eluant. The product was triturated in petrol
15   and the white solid isolated by filtration, washed with petrol and
dried in vacuo. There was thus obtained di-tert-butyl-N-[N-
(benzyloxycarbonyl)-L-γ-glutamyl]-L-proline (2.86 g),
m.p. 106-108°C.
NMR Spectrum: (CD$_3$SOCD$_3$) 1.37, 1.39 (2 x s, 18H, C(CH$_3$)$_3$),
20   1.62-2.10 (m, 6H, glu β-CH$_2$, proline 3- and 4-CH$_2$), 2.33 (m, 2H,
glu γ-CH$_2$), 3.42 (m, 2H, proline 5-CH$_2$), 3.93 (m, 1H, glu α-CH),
4.13, 4.40 (2 x dd, J = 8.8, 3.9 Hz, 1H, proline 2-CH),
5.03 (m, 2H, ArCH$_2$), 7.35 (m, 5H, ArH), 7.59 (t, 1H, glu NH).
Mass Spectrum: (CI) m/e 491 (M+H)$^+$.
25   Elemental Analysis: Found C, 63.39; H, 7.78; N, 5.69%.
C$_{26}$H$_{38}$N$_2$O$_7$ requires C, 63.65; H, 7.81; N, 5.71%.

A solution of di-tert-butyl-N-[N-(benzyloxycarbonyl)-
L-γ-glutamyl]-L-proline (0.98 g) in ethyl acetate containing
10% Pd/C (0.15 g) was stirred under hydrogen for 8 hours. The
30   catalyst was removed by filtration and the filtrate concentrated
in vacuo, yielding di-tert-butyl-L-γ-glutamyl-L-proline (0.70 g) as
an oil.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.37, 1.40 (2 x s, 18H, C(CH$_3$)$_3$),
1.55-2.10 (m, 6H, glu β-CH$_2$, proline 3- and 4-CH$_2$),
2.33 (t, J = 7.5 Hz, 2H, γ-CH$_2$), 3.16 (m, 1H, glu α-CH),
3.48 (t, J = 6.7 Hz, 2H, proline 5-CH$_2$), 4.14, 4.40 (2 x dd,
05   J = 8.8, 3.9 Hz, 1H, proline 2-CH).
Mass Spectrum: (CI) m/e 357 (M+H)$^+$.

(2) N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-L-proline.
        A mixture of N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-
10   ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid
salt (0.461 g) and di-tert-butyl-L-γ-glutamyl-L-proline (0.524 g)
was dissolved in dry dimethylformamide (15 ml) at 0°C and to this
solution was added diethyl cyanophosphonate (0.359 g) and then
triethylamine (0.222 g) under a nitrogen atmosphere. The solution
15   was stirred at 0°C and in the dark for 20 minutes and then at
laboratory temperature for 3 hours, then diluted with ethyl
acetate (100 ml) and water (100 ml). The water layer was separated
and extracted with ethyl acetate (2 x 100 ml). The combined ethyl
acetate extracts were washed with 10% aqueous citric acid
20   (2 x 50 ml), saturated sodium bicarbonate (100 ml) and dilute
aqueous sodium chloride (100 ml), then dried over anhydrous sodium
sulphate, filtered and concentrated in vacuo. The residue was
purified by chromatography on a silica gel column using ethyl
acetate as eluant. The product was precipitated from cold diethyl
25   ether/petrol and there was thus obtained di-tert-butyl-N-p-[N-(3,4-
dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-
benzoyl-L-γ-glutamyl-L-proline (0.192 g), m.p. 113-117°C.
NMR Spectrum: (CD$_3$SOCD$_3$) 1.31, 1.35, 1.39 (3 x s, 18H, C(CH$_3$)$_3$),
1.70-2.10 (m, 6H, glu β-CH$_2$, proline 3- and 4-CH$_2$), 2.32 (s, 3H,
30   quinazoline 2-CH$_3$), 2.38 (t, J = 7.5 Hz, 2H, glu γ-CH$_2$), 3.19 (s,
1H, C≡CH), 3.41 (m, 2H, proline 5-CH$_2$), 4.15, 4.40 (2 x dd,
J = 9.0, 3.8 Hz, 1H, proline 2-CH), 4.32 (m, 3H, CH$_2$C≡C, glu α-CH),

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4.77 (s, 2H, quinazoline 6-CH$_2$), 6.83 (d, J = 8.9 Hz, 2H,

3',5'-ArH), 7.53 (d, J = 8.4 Hz, 1H, quinazoline 8-H),

7.68 (dd, J = 8.4 Hz, 2.0 Hz, 1H, quinazoline 7-H),

7.73 (d, J = 9.0 Hz, 2H, 2',6'-ArH), 7.97 (d, J = 2.0 Hz, 1H,

05   quinazoline 5-H), 8.23 (t, 1H, NH).

Mass Spectrum: (positive ion FAB) m/e 708 (M+Na)$^+$.

Elemental Analysis: Found C, 65.81; H, 6.88; N, 10.00%.

C$_{38}$H$_{47}$N$_5$O$_7$·0.5H$_2$O requires C, 65.69; H, 6.96; N, 10.08%.

A mixture of di-_tert_-butyl-N-_p_-[N-(3,4-dihydro-2-methyl-

10   4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-

glutamyl-L-proline (0.067 g) and trifluoroacetic acid (5 ml) was

stirred at laboratory temperature for 1 hour in the dark. The

solution was then concentrated _in vacuo_ and the residue triturated

with diethyl ether (20 ml). The white solid was isolated by

15   filtration, washed with diethyl ether (4 x 10 ml) and dried

in vacuo. There was thus obtained N-_p_-[N-(3,4-dihydro-2-methyl-4-

oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-

glutamyl-L-proline, trifluoroacetate salt (0.054 g),

m.p. 162°C decomp.

20   NMR Spectrum: (CD$_3$SOCD$_3$) 1.84, 2.08 (2 x m, 6H, glu β-CH$_2$,

proline 3- and 4-CH$_2$), 2.39 (m, 5H, quinazoline 2-CH$_3$, glu γ-CH$_2$),

3.23 (s, 1H, C≡CH), 3.42 (m, 2H, proline 5-CH$_2$), 4.34 (m, 3H,

CH$_2$≡C, glu α-CH), 4.23, 4.48 (dd, J = 9.9, 3.5 Hz, 1H,

proline 2-CH), 4.80 (s, 2H, quinazoline 6-CH$_2$), 6.83 (d, J = 8.8 Hz,

25   2H, 3',5'-ArH), 7.57 (d, J = 8.4 Hz, 1H, quinazoline 8-H),

7.74 (d, J = 8.7 Hz, 3H, 2',6'-ArH, quinazoline 7-H),

7.99 (s, 1H, quinazoline 5-H), 8.32 (t, 1H, NH).

Mass Spectrum: (positive ion FAB) m/e 596 (M+Na)$^+$.

Elemental Analysis: Found C, 55.44; H, 4.91; N, 9.81%.

30   C$_{30}$H$_{31}$N$_5$O$_7$·1.1CF$_3$CO$_2$H 0.22Et$_2$O requires C, 55.54; H, 4.83;

N, 9.79%.

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Example 4: N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-α-
methylalanine.

(1) Di-tert-butyl-L-γ-glutamyl-α-methylalanine.

05   α-Aminoisobutyric acid (6.18 g), tert-butyl acetate (200 ml)
and 70% aqueous perchloric acid (9.45 g) were stirred at laboratory
temperature for 7 days. The mixture was then cooled in an ice-water
bath and extracted with 0.5 N hydrochloric acid (4 x 50 ml). The
combined aqueous extracts were immediately neutralised with solid
10   sodium bicarbonate. The aqueous solution was extracted with
diethyl ether (3 x 100 ml), the ether extracts pooled, dried over
anhydrous sodium sulphate and the ether evaporated in vacuo to give
tert-butyl α-methylalanine (4.98 g).
NMR Spectrum: (CD$_3$SOCD$_3$) 1.16 (s, 6H, C(CH$_3$)$_2$),
15   1.40 (s, 9H, C(CH$_3$)$_3$).

        To a stirred solution of α-tert-butyl-N-benzyloxycarbonyl-L-
glutamate (3.033 g) and N-methylmorpholine (0.909 g) in dry
tetrahydrofuran (10 ml) cooled to -20°C was added isobutyl
chloroformate (1.224 g). After 10 minutes a solution of tert-butyl
20   α-methylalanine (2.0 g) in tetrahydrofuran (5 ml) was added.
Stirring was continued for 10 minutes at -20°C, and then at
laboratory temperature for 1 hour. N-Methylmorpholine hydrochloride
was filtered off and the filtrate concentrated in vacuo. The
residue was purified by chromatography on a silica gel column
25   using 2% methanol in dichloromethane as eluant. The product was
crystallised from diethyl ether/petrol and the white solid isolated
by filtration, washed with petrol and dried in vacuo. There was
thus obtained di-tert-butyl [N-(benzyloxycarbonyl)-L-γ-glutamyl]-
L-α-methylalanine (3.855 g), m.p. 109-110°C.
30   NMR Spectrum: (CD$_3$SOCD$_3$) 1.27 (s, 6H, C(CH$_3$)$_2$), 1.34,
1.39 (2 x s, 18H, C(CH$_3$)$_3$), 1.73, 1.90 (2 x m, 2H, β-CH$_2$),
2.13 (t, J = 7.3 Hz, 2H, γ-CH$_2$), 3.90 (m, 1H, glu α-CH),
5.03 (m, 2H, ArCH$_2$), 7.36 (m, 5H, ArH), 7.64 (d, J = 7.5 Hz,
1H, glu NH), 8.06 (s, 1H, α-methylalanine NH).

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Mass Spectrum: (positive ion FAB) m/e 501 (M+Na)$^+$.

Elemental Analysis: Found C, 62.73; H, 8.02; N, 5.82%.

$C_{25}H_{38}N_2O_7$ Requires: C, 62.74; H, 8.00; N, 5.85%.

05   A solution of the product (0.669 g) in ethyl acetate containing
10% Pd/C (0.2 g) was stirred under hydrogen for 3 hours. The
catalyst was removed by filtration and the filtrate concentrated
in vacuo, yielding di-tert-butyl-L-γ-glutamyl-α-methylalanine
(0.541 g) as an oil.

(2) N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
10   N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-α-methylalanine.

The process described in Example 1(3) was repeated using
di-tert-butyl-L-γ-glutamyl-α-methylalanine (0.541 g) as starting
material in place of tri-tert-butyl-L-γ-glutamyl-N-methyl-L-
glutamate. There was thus obtained di-tert-butyl-N-p-[N-(3,4-
15   dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)-
amino]benzoyl-L-γ-glutamyl-α-methylalanine (0.486 g),
m.p. 115-116°C.

NMR Spectrum: (CD_3SOCD_3) 1.26 (s, 6H, $C(CH_3)_2$), 1.33, 1.39 (2 x s,
18H, $C(CH_3)_3$), 1.91, 1.99 (2 x m, 2H, β-CH_2), 2.14 (m, 2H, γ-CH_2),
20   2.32 (s, 3H, quinazoline 2-CH_3), 3.27 (s, 1H, C≡CH), 4.25 (m, 1H,
glu α-CH), 4.34 (s, 2H, CH_2C≡C), 4.78 (s, 2H, quinazoline 6-CH_2),
6.83 (d, J = 8.9 Hz, 2H, 3',5'-ArH), 7.54 (d, J = 8.4 Hz, 1H,
quinazoline 8-H), 7.70 (dd, J = 2.0 Hz, 1H, quinazoline 7-H),
7.74 (d, J = 8.8 Hz, 2H, 2',6'-ArH), 7.96 (d, J = 1.6 Hz, 1H,
25   quinazoline 5-H), 8.07 (s, 1H, α-methylalanine NH),
8.34 (d, J = 7.4 Hz, 1H, glu NH), 12.20 (s, 1H, lactam NH).

Mass Spectrum: (positive ion FAB) m/e 674 (M+H)$^+$.

Elemental Analysis: Found C, 65.05; H, 7.04; N, 10.18%.

$C_{37}H_{47}N_5O_7 \cdot 0.5H_2O$ requires C, 65.08; H, 7.09; N, 10.26%.

30   Di-tert-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-α-methylalanine
(0.1 g) was treated with trifluoroacetic acid as described in
Example 1(3). There was thus obtained N-p-[N-(3,4-dihydro-2-methyl-
4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-
35   glutamyl-α-methylalanine (0.062 g), m.p. 155-158°C.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.29 (s, 6H, C(CH$_3$)$_2$), 1.89, 2.02 (2 x m,
2H, β-CH$_2$), 2.18 (m, 2H, γ-CH$_2$), 2.38 (s, 3H, quinazoline 2-CH$_3$),
3.23 (s, 1H, C≡CH), 4.29 (m, 1H, glu α-CH), 4.34 (s, 2H, CH$_2$C≡C),
4.80 (s, 2H, quinazoline 6-CH$_2$), 6.83 (d, J = 8.3 Hz, 2H,

05   3',5'-ArH), 7.57 (d, J = 8.3 Hz, 1H, quinazoline 8-H),
7.75 (d, J = 8.1 Hz, 3H, 2',6'-ArH and quinazoline 7-H),
7.98 (s, 1H, quinazoline 5-H), 8.02 (s, 1H, α-methylalanine NH),
8.29 (d, J = 7.6 Hz, 1H, glu NH), 12.40 (br, CO$_2$H).
Mass Spectrum: (positive ion FAB) m/e 584 (M+Na)$^+$.

10   Elemental Analysis: Found C, 55.21; H, 5.00; N, 10.57; F, 5.80%.
C$_{29}$H$_{31}$N$_5$O$_7$.0.7CF$_3$CO$_2$H.1H$_2$O requires C, 55.37; H, 5.15; N, 10.62;
F, 6.05%.

Example 5 : N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-4-methylglutamyl-L-

15   glutamic acid.

(1) α-tert-Butyl-γ-methyl-N-trityl-L-4-methylglutamate.
γ-Methyl-L-glutamate (12.88 g), tert-butyl acetate (500 ml)
and 70% aqueous perchloric acid (12.6 g) were stirred at room
temperature for 88 hours. The mixture was then cooled in an

20   ice-water bath and extracted with cold 0.5 N hydrochloric acid
(3 x 130 ml). The combined aqueous extracts were immediately
neutralised with solid sodium bicarbonate and then extracted with
diethyl ether (3 x 200 ml). The ether extracts were combined,
dried over anhydrous sodium sulphate, filtered and the solution

25   concentrated in vacuo to give α-tert-butyl-γ-methyl-L-glutamate
(14.5 g) as a colourless oil.
To a stirred solution of α-tert-butyl-γ-methyl-L-glutamate
(13.71 g) in dry chloroform (50 ml), triethylamine (8.49 g) was
added followed by lead nitrate (8.34 g) and then a solution of

30   trityl chloride (11.67 g) in dry chloroform (20 ml). After
stirring at room temperature for 18 hours a white solid had
precipitated from the solution. This was removed by filtration,
the filtrate concentrated in vacuo and the orange residue purified

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by chromatography on a silica gel column using a gradient of
dichloromethane in hexane (10-100%) as eluant. There was thus
obtained α-<u>tert</u>-butyl-γ-methyl-<u>N</u>-trityl-L-glutamate (9.46 g) as an
oil, which solidified on standing at -20°C for 4 weeks,

05. m.p. 79-80°C.

NMR Spectrum: (CD$_3$SOCD$_3$) 1.13 (s, 9H, C(CH$_3$)$_3$), 1.80,
1.92 (2 x m, 2H, β-CH$_2$), 2.18, 2.44 (2 x m, 2H, γ-CH$_2$),
2.79 (d, J = 9.0 Hz, 1H, NH), 3.17 (m, 1H, α-CH),
3.60 (s, 3H, OCH$_3$), 7.16-7.41 (m, 15H, TrH).

10 Mass Spectrum: (CI) m/e 460 (M+H)$^+$.

Elemental Analysis: Found C, 76.13; H, 7.29; N, 2.89%.
C$_{29}$H$_{33}$NO$_4$ requires C, 75.79; H, 7.24; N, 3.05%.

To a stirred solution of 0.6 M potassium hexamethyldisilazide
in tetrahydrofuran (13.75 ml) at -78°C and under argon was added a

15 solution of α-<u>tert</u>-butyl-γ-methyl-<u>N</u>-trityl-L-glutamate (2.52 g), in
dry tetrahydrofuran (25 ml) over a 5 minute period. The resulting
yellow solution was stirred at -78°C for 50 minutes and then methyl
iodide (1.56 g) was added. Stirring was continued at -78°C for
1.25 hours and the white slurry was then poured into a saturated

20 solution of ammonium chloride (200 ml). The mixture was extracted
with diethyl ether (2 x 200 ml), the ether extracts were combined,
dried over anhydrous sodium sulphate, filtered and the solution
concentrated <u>in vacuo</u>. The residue was purified by chromatography
on a silica gel column using a gradient of ethyl acetate in hexane

25 (3-9%) as eluant. There was thus obtained α-<u>tert</u>-butyl-γ-methyl-
<u>N</u>-trityl-L-4-methylglutamate (1.62 g) as a viscous oil, being a
mixture of the two diastereoisomers (2S, 4S and 2S, 4R).

NMR Spectrum: (CD$_3$SOCD$_3$) 0.98, 1.04 (2 x d, J = 7.0 Hz, 3H,
γ-CH$_3$), 1.12, 1.14 (2 x s, 9H, C(CH$_3$)$_3$), 1.38, 1.54 (2 x m, 1H,

30 β-CH), 1.93, 2.10 (2 x m, 1H, β-CH), 2.40 (m, 1H, γ-CH), 2.75,
2.80 (2 x d, J$_1$ = 8.9 Hz, J$_2$ = 9.4 Hz, 1H, NH), 3.10 (m, 1H, α-CH),
3.50, 3.66 (2 x s, 3H, CO$_2$CH$_3$), 7.16-7.39 (m, 15H, TrH).

Mass Spectrum: (CI) m/e 474 (M+H)$^+$.

Elemental Analysis: Found C, 76.12; H, 7.61; N, 2.89%.
C$_{30}$H$_{35}$NO$_4$ requires C, 76.08; H, 7.45; N, 2.96%.

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(2) Tri-tert-butyl-L-γ-4-methylglutamyl-L-glutamate

To a mixture of lithium hydroxide monohydrate (0.117 g) in
water (1.86 ml) was added a solution of α-tert-butyl-γ-methyl-N-
trityl-L-4-methylglutamate (1.1 g) in tetrahydrofuran (27 ml). The
05   resulting mixture was refluxed for 3 hours, then more water (0.6 ml)
was added and refluxing continued for 5 hours. The organic solvent
was then removed by evaporation, the residue was treated with a
saturated sodium bicarbonate solution (100 ml) and the resulting
mixture was acidified to pH 6 using dilute hydrochloric acid. The
10   mixture was extracted with ethyl acetate (2 x 100 ml), the extracts
combined, dried over anhydrous sodium sulphate, filtered and
concentrated in vacuo. The residue was dried over phosphorus
pentoxide in a vacuum dessicator overnight to give
α-tert-butyl-N-trityl-L-4-methylglutamate (1.06 g) as a white foam.
15   To a stirred solution of α-tert-butyl-N-trityl-L-4-
methylglutamate (0.76 g) and N-methylmorpholine (0.151 g) in dry
tetrahydrofuran (3.5 ml) cooled to -20°C was added isobutyl
chloroformate (0.204 g). After 10 minutes a mixture of
di-tert-butyl-L-glutamate hydrochloride (0.442 g) and
20   N-methylmorpholine (0.151 g) in dry tetrahydrofuran (4.5 ml) was
added. Stirring was continued at -20°C for 10 minutes and then
for 1.5 hours while the mixture was allowed to warm to room
temperature. N-Methylmorpholine hydrochloride was filtered off and
the filtrate concentrated in vacuo. The residue was purified by
25   chromatography on a silica gel column using a gradient of ethyl
acetate in distilled petrol (7-20%) as eluant. The product
solidified on drying over phosphorus pentoxide in vacuo overnight.
There was thus obtained tri-tert-butyl-N-[N-(trityl)-L-γ-4-methyl-
glutamyl]-L-glutamate (0.669 g), m.p. 58-66°C.
30   NMR Spectrum: (CD$_3$SOCD$_3$) 0.94 (d, J = 6.8 Hz, 3H, 4-Meglu γ-CH$_3$),
1.14 (s, 9H, 4-Meglu C(CH$_3$)$_3$), 1.39 (m, 19H, glu C(CH$_3$)$_3$ and
4-Meglu β-CH), 1.85, 2.11 (2 x m, 3H, 4-Meglu β-CH and glu β-CH$_2$),
2.27 (t, J = 7.6 Hz, 2H, glu γ-CH$_2$), 2.38 (m, 1H, 4-Meglu γ-CH),
2.68 (d, J = 9.0 Hz, 1H, 4-Meglu NH), 3.04 (m, 1H, 4-Meglu α-CH),
35   4.13 (m, 1H, glu α-CH), 7.14-7.41 (m, 15H, TrH),
8.14 (d, J = 7.4 Hz, 1H, glu NH).

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Mass Spectrum: (CI) m/e 701 (M+H)$^+$.

Elemental Analysis: Found C, 72.02; H, 8.02, N, 3.87%.

$C_{42}H_{56}N_2O_7$ requires C, 71.97; H, 8.05; N, 4.00%.

A solution of tri-<u>tert</u>-butyl-<u>N</u>-[<u>N</u>-(trityl)-L-γ-4-methyl-
05 glutamyl]-L-glutamate (0.608 g) in ethyl acetate (60 ml) containing
10% Pd/C (0.160 g) was stirred under hydrogen for 26 hours. Then
more catalyst (0.035 g) was added and stirring continued under
hydrogen for 20 hours. The catalyst was removed by filtration and
the filtrate concentrated <u>in vacuo</u> to give a white semisolid, a
10 mixture of triphenylmethane and tri-<u>tert</u>-butyl-L-γ-4-methyl-
glutamyl-L-glutamate (0.450 g).

(3) <u>N</u>-<u>p</u>-[<u>N</u>-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
<u>N</u>-(prop-2-ynyl)amino]benzoyl-L-γ-4-methylglutamyl-L-glutamic acid.

To a stirred solution of tri-<u>tert</u>-butyl-L-γ-4-methylglutamyl-L-
15 glutamate (0.430 g) in dry dimethylformamide (6.5 ml) cooled to 0°C
was added <u>p</u>-[<u>N</u>-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
<u>N</u>-(prop-2-ynyl)amino]benzoic acid, trifluoroacetate salt (0.327 g),
then diethyl cyanophosphonate (0.231 g) and triethylamine
(0.143 g). The resulting solution was stirred in the dark at 0°C
20 for 30 minutes and then for 1.5 hours at room temperature.
Ethyl acetate (100 ml) and water (100 ml) were then added to the
reaction mixture. The two layers were separated and the aqueous
layer extracted with more ethyl acetate (2 x 100 ml). The combined
ethyl acetate extracts were washed with 10% aqueous citric acid
25 (2 x 100 ml), a saturated sodium bicarbonate solution (150 ml), a
dilute aqueous sodium chloride solution (150 ml), water (100 ml)
and then dried over anhydrous sodium sulphate, filtered and the
ethyl acetate removed <u>in vacuo</u>. The residue was purified by
chromatography on a silica gel column using a gradient of methanol
30 in ethyl acetate (0-2%) as eluant. The product was precipitated
from diethyl ether/petroleum ether at -20°C and there was thus
obtained tri-<u>tert</u>-butyl-<u>N</u>-<u>p</u>-[<u>N</u>-(3,4-dihydro-2-methyl-4-
oxoquinazolin-6-ylmethyl)-<u>N</u>-(prop-2-ynyl)amino]benzoyl-L-γ-4-
methylglutamyl-L-glutamate (0.170 g), m.p. 102-110°C.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.03 (d, J = 6.81 Hz, 3H, 4-Meglu γ-CH$_3$),
1.33, 1.36, 1.38 (3 x s, 27H, C(CH$_3$)$_3$), 1.65, 1.83, 2.05 (3 x m,
4H, β-CH$_2$), 2.20 (t, J = 7.7 Hz, 2H, glu γ-CH$_2$), 2.32 (s, 3H,
quinazoline 2-CH$_3$), 2.50 (m, DMSO peak and 4-Meglu γ-CH),
05   3.22 (s, 1H, C≡CH), 4.07 (m, 1H, glu α-CH), 4.21 (m, 1H, 4-Meglu
α-CH), 4.34 (s, 2H, CH$_2$C≡C), 4.78 (s, 2H, quinazoline 6-CH$_2$),
6.82 (d, J = 8.7 Hz, 2H, 3',5'-ArH), 7.54 (d, J = 8.4 Hz, 1H,
quinazoline 8-H), 7.68 (m, 3H, quinazoline 7-H and 2',6'-ArH),
7.96 (s, 1H, quinazoline 5-H), 8.06 (d, J = 7.6 Hz, 1H, glu NH),
10   8.20 (d, J = 7.7 Hz, 1H, 4-Meglu$_L$ NH) 12.18 (s, 1H, lactam NH).
Mass Spectrum: (ESI) m/e 788 (M+H)$^+$.
Elemental Analysis: Found C, 64.91; H, 7.27; N, 8.79%.
C$_{43}$H$_{57}$N$_5$O$_9$.0.5H$_2$O requires C, 64.81; H, 7.33; N, 8.79%.

   Tri-tert-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-
15   ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-4-methylglutamyl-L-
glutamate (0.071 g) was treated with trifluoroacetic acid (6 ml) as
described in Example 1(3) for the L-γ-glutamyl-N-methyl-L-glutamate
analogue. There was thus obtained N-p-[N-(3,4-dihydro-2-methyl-4-
oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-4-
20   methylglutamyl-L-glutamic acid (containing 0.95 equivalents of
trifluoroacetic acid, 0.4 equivalents of diethyl ether
and 1.2 equivalents of water; 0.053 g), m.p. 160-165°C (dec).
NMR Spectrum: 1.02 (d, J = 6.8 Hz, 3H, 4-Meglu γ-CH$_3$), 1.65, 1.91,
2.09 (3 x m, 4H, β-CH$_2$), 2.25 (t, J = 7.6 Hz, 2H, glu γ-CH$_2$),
25   2.39 (s, 3H, quinazoline 2-CH$_3$), 2.50 (DMSO peak and 4-Meglu γ-CH),
3.23 (s, 1H, C≡CH), 4.19 (m, 2H, glu α-CH and 4-Meglu α-CH),
4.35 (s, 2H, CH$_2$C≡CH), 4.80 (s, 2H, quinazoline 6-CH$_2$),
6.82 (d, J = 8.9 Hz, 2H, 3',5'-ArH), 7.58 (d, J = 8.,4 Hz, 1H,
quinazoline 8-H), 7.74 (d, J = 8.7 Hz, 3H, quinazoline 7-H and
30   2',6'-ArH), 7.99 (s, 1H, quinazoline 5-H), 8.10 (d, J = 7.7 Hz, 1H,
glu NH), 8.26 (d, J = 7.7 Hz, 1H, 4-Meglu NH).
Mass Spectrum: (ESI) m/e 620 (M+H)$^+$.
Elemental Analysis: Found C, 53.05; H, 5.46; N, 8.97; F, 6.89%.
C$_{31}$H$_{33}$N$_5$O$_9$·0.95 CF$_3$COOH·0.4Et$_2$O·1.2H$_2$O requires C, 53.18; H, 5.22;
35   N, 8.99; F.6.95%.

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Example 6 : N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-4,4-dimethylglutamyl-
L-glutamic acid.

(1) α-tert-Butyl-γ-allyl-N-trityl-L-4,4-dimethylglutamate.

05   To a stirred suspension of L-glutamic acid (8.82 g) in dry
allyl alcohol (300 ml) chlorotrimethylsilane (19 ml) was added
dropwise under an argon atmosphere. The mixture was stirred at
room temperature for 18 hours and then diethyl ether (2 litres) was
added to give a white precipitate. This was collected by
10   filtration, washed with more diethyl ether and dried in vacuo over
phosphorus pentoxide. There was thus obtained γ-allyl-L-glutamate
hydrochloride (10.1 g) as as white solid, m.p. 132-133°C (decomp).
NMR Spectrum: (CD_3SOCD_3) 2.05 (m, 2H, β-CH_2), 2.54 (m, 2H, γ-CH_2),
3.90 (t, J = 6.3 Hz, 1H, α-CH), 4.55 (dm, J = 5.4 Hz, 2H,
15   CH_2CH=CH_2), 5.20 (dm, J = 9.3 Hz, 1H, CH=CH_2 cis),
5.30 (dm, J = 16.3 Hz, 1H, CH=CH_2 trans), 5.93 (m, 1H, CH=CH_2),
8.52 (bd s, 3H, NH_3).
Mass Spectrum: (CI) m/e 188 (M-Cl).
        γ-Allyl-L-glutamate hydrochloride (8.94 g), t-butyl acetate
20   (250 ml) and 70% aqueous perchloric acid (6.3 g) were stirred at
room temperature for 100 hours. The mixture was then cooled in an
ice-water bath and extracted with cold 0.5 N hydrochloric acid
(3 x 80 ml). The combined aqueous extracts were immediately
neutralised using solid sodium bicarbonate and then extracted with
25   diethyl ether (3 x 120 ml). The extracts were combined, dried over
anhydrous sodium sulphate, filtered and concentrated in vacuo to
give α-tert-butyl-γ-allyl-L-glutamate (10.0 g) as a colourless oil.
        To a stirred solution of α-tert-butyl-γ-allyl-L-glutamate
(8.4 g) in dry chloroform (35 ml), triethylamine (5.25 g) was added
30   followed by a solution of trityl chloride (7.23 g) in chloroform
(15 ml) and then lead nitrate (4.3 g). After stirring at room
temperature for 17 hours a white solid had formed. The solid was
removed by filtration, the filtrate concentrated in vacuo and the
residue was treated with hexane (40 ml) and left in a fridge

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overnight. The hexane solution was then filtered, the filtrate
concentrated in vacuo and the residue purified by chromatography on
a silica gel column using a gradient of ethyl acetate in distilled
petroleum ether (4-6%) as eluant. There was thus obtained
05   α-tert-butyl-γ-allyl-N-trityl-L-glutamate (8.10 g) as a yellow oil.
NMR Spectrum: (CD$_3$SOCD$_3$) 1.13 (s, 9H, C(CH$_3$)$_3$), 1.80,
1.90 (2 x m, 2H, β-CH$_2$), 2.20, 2.46 (2 x m, 2H, γ-CH$_2$),
2.80 (d, J = 9.0 Hz, 1H, NH), 3.17 (m, 1H, α-CH),
4.54 (d, J = 5.5 Hz, 2H, CO$_2$CH$_2$CH=CH$_2$), 5.20 (dm, J = 10.4 Hz, 1H,
10   CH=CH$_2$ cis), 5.29 (dm, J = 15.8 Hz, 1H, CH=CH$_2$ trans), 6.88 (m, 1H,
CH=CH$_2$), 7.15-7.40 (m, 15H, TrH).
Mass Spectrum: (CI) m/e 486 (M+H)$^+$.
Elemental Analysis: Found C, 76.46; H, 7.39; N, 2.82%.
C$_{31}$H$_{35}$NO$_4$ requires C, 76.67; H, 7.26; N, 2.88%.

15   To a stirred solution of potassium hexamethyldisilazide
(23.68 ml, 0.5 M in toluene) in dry tetrahydrofuran (22 ml)
at -78°C and under argon was adeed a solution of α-tert-butyl-γ-
allyl-N-trityl-L-glutamate (3.59 g) in dry tetrahydrofuran (26 ml)
over a 5 minute period. The resulting yellow solution was stirred
20   at -78°C for 55 minutes and then methyl iodide (2.10 g) was added.
Stirring was continued at -78°C for 30 minutes and then the white
slurry was poured into a saturated solution of ammonium chloride
(200 ml). The resulting mixture was extracted with diethyl ether
(3 x 150 ml), the ether extracts combined, dried over anhydrous
25   sodium sulphate, filtered and concentrated in vacuo. The residue
was purified by chromatography on a silica gel column using a
gradient of ethyl acetate in petroleum ether (6-8%) as eluant.
There was thus obtained α-tert-butyl-γ-allyl-N-trityl-L-4-
methylglutamate (3.26 g) as an oil, being a mixture of the two
30   diastereoisomers (2S, 4S) and (2S, 4R).
NMR Spectrum: (CD$_3$SOCD$_3$) 1.00, 1.07 (2 x d, J = 7.0 Hz, 3H,
γ-CH$_3$), 1.12, 1.15 (2 x s, 9H, C(C':)$_3$), 1.38, 1.57 (2 x m, 1H,
β-CH), 1.95, 2.15 (2 x m, 1H, β-CH), 2.45 (m, 1H, γ-CH),

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2.80 (t, J = 9.4 Hz, 1H, NH), 3.12 (m, 1H, α-CH), 4.43 (ABdd,
J_1 = 13.7 Hz, J_2 = 5.4 Hz, 1H, C$\underline{H}_2$CH=CH$_2$), 4.60 (d, J = 5.3 Hz, 1H,
C$\underline{H}_2$CH = CH$_2$), 5.10-5.35 (m, 2H, CH=C$\underline{H}_2$), 5.70-6.00 (m, 1H, C$\underline{H}$=CH$_2$),
7.16-7.40 (m, 15H, TrH).

05   Mass Spectrum: (CI) m/e 500 (M+H)$^+$.

Elemental Analysis: Found C, 75.74; H, 7.47; N, 2.73%.

$C_{32}H_{37}NO_4 \cdot 0.4H_2O$ requires C, 75.83; H, 7.52; N, 2.76%.

To a stirred solution of potassium hexamethyldisilazide
(16.2 ml, 0.5 M in toluene) in dry tetrahydrofuran (16 ml)

10   at -78°C and under argon was added a solution of α-tert-γ-allyl-N-
trityl-L-4-methylglutamate (2.24 g) in dry tetrahydrofuran (16 ml)
over a 5 minute period. The resulting yellow solution was stirred
at -78°C for 55 minutes and then methyl iodide (1.12 ml) was
added. Stirring was continued at -78°C for 2 hours and then the

15   yellow slurry was poured into a saturated solution of ammonium
chloride (200 ml). The aqueous solution was extracted with diethyl
ether (3 x 150 ml), the ether extracts combined, dried over
anhydrous sodium sulphate, filtered and the solution concentrated
in vacuo. The residue was purified by chromatography on a silica

20   gel column using a gradient of ethyl acetate in distilled petroleum
ether (3-6%). There was thus obtained α-tert-butyl-γ-allyl-N-
trityl-L-4,4-dimethylglutamate (2.08 g) as a colourless oil.

NMR Spectrum: (CD$_3$SOCD$_3$) 0.94, 0.96 (2 x s, 6H, γ-CH$_3$),
1.20 (s, 9H, C(CH$_3$)$_3$), 1.34 (dd, J_1 = 14.2 Hz, J_2 = 3.7 Hz, 1H,

25   β-CH), 2.06 (dd, J_1 = 14.3 Hz, J_2 = 8.6 Hz, 1H, β-CH),
2.78 (d, J = 8.9 Hz, 1H, NH), 3.09 (m, 1H, α-CH), 4.50 (ABddd,
J_1 = 15.0 Hz, J_2 = 5.0 Hz, J_3 = 1.2 Hz, 2H, C$\underline{H}_2$CH=CH$_2$),
5.16-5.30 (m, 2H, CH=C$\underline{H}_2$), 5.87 (m, 1H, C$\underline{H}$=CH$_2$),
7.16-7.40 (m, 15H, TrH).

30   Mass Spectrum: (CI) m/e 514 (M+H)$^+$.

Elemental Analysis: Found C, 75.96; H, 7.61; N, 2.66%.

$C_{33}H_{39}NO_4 \cdot 0.5H_2O$ requires C, 75.83; H, 7.71; N, 2.68%.

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(2) Tri-tert-butyl-L-γ-4-dimethylglutamyl-L-glutamate.

   To a stirred solution of α-tert-butyl-γ-allyl-N-trityl-L-4,4-
dimethylglutamate (1.4 g) in dry dichloromethane (11 ml) under
argon was added tetrakis(triphenylphosphine)palladium(0) (0.091 g)
05   and then pyrrolidine (0.35 ml). The resulting yellow solution was
stirred at room temperature for 20 minutes and then diethyl ether
(100 ml) and 1N hydrochloric acid (50 ml) were added. The two
layers were separated and the aqueous layer washed with more
diethyl ether (100 ml). The ether extracts were combined, dried
10   over anhydrous sodium sulphate, filtered and concentrated in vacuo.
The residue was treated with diethyl ether (30 ml), the yellow
precipitate filtered off and the filtrate concentrated in vacuo to
give α-tert-butyl-N-trityl-L-4,4- dimethylglutamate (1.25 g) as a
white foam.
15   To a stirred solution of α-tert-butyl-N-trityl-L-4,4-
dimethylglutamate (0.710 g) and (1H-1,2,3-benzotriazol-1-yloxy)-
tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP) (0.935 g)
in dry dichloromethane (1.9 ml) was added diisopropylethylamine
(0.464 g) and then 4-dimethylaminopyridine (0.109 g) and
20   di-tert-butyl-L-glutamate hydrochloride (0.531 g). After stirring
at room temperature for 3 hours the solvent was removed by
evaporation and the yellow residue purified by chromatography on a
silica gel column using a gradient of ethyl acetate in hexane
(5-20%) as eluant. There was thus obtained
25   tri-tert-butyl-N-[N-(trityl-γ-4,4- dimethylglutamyl]-L-glutamate
(0.445 g) as an oil.
NMR Spectrum: 0.80, 0.95 (2 x s, 6H, 2 x γ-CH$_3$), 1.19 (s, 9H,
4-diMeglu C(CH$_3$)$_3$), 1.34 (s, 9H, glu C(CH$_3$)$_3$), 1.39 (m, 10H,
glu C(CH$_3$)$_3$ and 4-diMeglu β-CH), 1.78-1.98 (m, 3H, glu β-CH$_2$ and
30   4-diMeglu β-CH), 2.22 (t, J = 7.2 Hz, 2H, glu γ-CH$_2$), 2.80 (d,
J = 8.2 Hz, 1H, 4-diMeglu NH), 2.98 (m, 1H, 4-diMeglu α-CH),
4.04 (m, 1H, glu α-CH), 7.14-7.40 (m, 15H, TrH).
Mass Spectrum: (CI) m/e 715 (M+H)$^+$.
Elemental Analysis: Found C, 71.65; H, 8.22; N, 3.84%.
35   C$_{43}$H$_{58}$N$_2$O$_7$·0.3H$_2$O requires C, 71.70; H, 8.20; N, 3.89%.

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A solution of tri-_tert_-butyl-_N_-[_N_-(trityl-L-γ-4,4-dimethyl-
glutamyl]-L-glutamate (0.430 g) in ethyl acetate (50 ml) containing
10% Pd/C (0.065 g) was stirred under hydrogen for 26 hours. Then
more catalyst (0.075 g) was added and stirring was continued under
05   hydrogen for 16 hours. The catalyst was removed by filtration and
the filtrate was concentrated _in vacuo_ to give a white semisolid, a
mixture of triphenylmethane and tri-_tert_-butyl-L-γ-4,4-dimethyl-
glutamyl-L-glutamate (0.400 g).

(3) _N_-_p_-[_N_-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
10   _N_-(prop-2-ynyl)amino]benzoyl-L-γ-4,4-dimethylglutamyl-L-glutamic
acid.

To a stirred solution of tri-_tert_-butyl-L-γ-4,4-dimethyl-
glutamyl-L-glutamate (0.360 g) in dry dimethylformamide (7.0 ml)
cooled to 0°C under argon was added _p_-[_N_-(3,4-dihydro-2-methyl-4-
15   oxoquinazolin-6-ylmethyl)-_N_-(prop-2-ynyl)amino]benzoic acid,
trifluoroacetate salt (0.200 g) followed by diethyl cyanophosphonate
(0.154 g) and triethylamine (0.095 g). The resulting solution was
stirred in the dark at 0°C for 10 minutes and then for 1.5 hours at
room temperature. Ethyl acetate (70 ml) and water (70 ml) were
20   then added to the reaction mixture. The two layers were separated
and the aqueous layer was extracted with more ethyl acetate
(2 x 50 ml). The combined ethyl acetate extracts were washed with
a 10% aqueous citric acid solution (100 ml), saturated sodium
bicarbonate solution (100 ml), dilute aqueous sodium chloride
25   solution (100 ml) and water (100 ml), then dried over anhydrous
sodium sulphate, filtered and concentrated _in vacuo_. The residue
was purified by chromatography on a silica gel column using a
gradient of methanol in ethyl acetate (0-2%) as eluant. The
product was precipitated from diethyl ether/petroleum ether
30   at -20°C yielding tri-_tert_-butyl-_N_-_p_-[_N_-(3,4-dihydro-2-methyl-4-
oxoquinazolin-6-ylmethyl)-_N_-(prop-2-ynyl)amino]benzoyl-L-γ-4,4-
dimethylglutamyl-L-glutamate (0.200 g) as a white powder,
m.p. 101-104°C.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.11, 1.16 (2 x s, 6H, 4-diMeglu γ-CH$_3$), 1.30, 1.36 (2 x s, 27H, C(CH$_3$)$_3$), 1.95 (m, 4H, β-CH$_2$), 2.21 (t, J = 7.7 Hz, 2H, glu γ-CH$_2$), 2.32 (s, 3H, quinazoline 2-CH$_3$), 3.22 (s, 1H, C≡CH), 4.08 (m, 1H, glu α-CH), 4.23 (m, 1H,

05   4-diMeglu α-CH), 4.31 (s, 2H, CH$_2$C≡C), 4.76 (s, 2H, quinazoline 6-CH$_2$), 6.81 (d, J = 8.7 Hz, 2H, 3',5'-ArH), 7.52 (d, J = 8.4 Hz, 1H, quinazoline 8-H), 7.66 (m, 4H, quinazoline 7-H, 2',6'-ArH and 4-diMeglu NH), 7.95 (s, 1H, quinazoline 5-H), 8.19 (d, J = 7.3 Hz, 1H, glu NH), 12.19 (s, 1H, lactam NH).

10   Mass Spectrum: (ESI) m/e 801 (M$^+$).

Elemental Analysis: Found C, 66.03; H, 7.68; N, 8.50%.

C$_{44}$H$_{59}$N$_5$O$_9$ requires C, 65.90; H, 7.41; N, 8.73%.

Tri-_tert_-butyl-_N_-_p_-[_N_-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-_N_-(prop-2-ynyl)amino]benzoyl-L-γ-4,4-dimethylglutamyl-L-

15   glutamate (0.068 g) was treated with trifluoroacetic acid (7 ml) as described in Example 1(3) for the L-γ-glutamyl-_N_-methyl-L-glutamate analogue. There was thus obtained _N_-_p_-[_N_-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-_N_-(prop-2-ynyl)amino]benzoyl-L-γ-4,4-dimethylglutamyl-L-glutamic acid (containing 0.6 equivalents of trifluoroacetic acid and 0.8 equivalents of water; 0.050 g),

20   m.p. >140°C (dec).

NMR Spectrum (CD$_3$SOCD$_3$): 1.12, 1.17 (2 x s, 6H, 4-diMeglu γ-CH$_3$), 1.84-2.13 (m, 4H, β-CH$_2$), 2.25 (t, J = 7.4 Hz, 2H, glu γ-CH$_2$), 2.38 (s, 3H, quinazoline 2-CH$_3$), 3.23 (s, 1H, C≡CH), 4.20 (m, 1H,

25   glu α-CH), 4.33 (m, 3H, CH$_2$C≡CH and 4-diMeglu α-CH), 4.79 (s, 2H, quinazoline 6-CH$_2$), 6.82 (d, J = 8.6 Hz, 2H, 3',5'-ArH), 7.57 (d, J = 8.4 Hz, 1H, quinazoline 8-H), 7.71 (m, 4H, quinazoline 7-H, 2',6'-ArH and 4-diMeglu NH), 7.99 (s, 1H, quinazoline 5-H), 8.22 (d, J = 7.30 Hz, 1H, glu NH).

30   Mass Spectrum: (ESI) m/e 634 (M+H)$^+$.

Elemental Analysis: Found C, 55.71; H, 5.41; N, 9.60; F, 4.64%.

C$_{32}$H$_{35}$N$_5$O$_9$·0.6TFA·0.8H$_2$O requires C, 55.66; H, 5.23; N, 9.77; F, 4.77%.

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Example 7 : N-p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid.

The process described in Example 1(3) was repeated using
05 N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid salt (0.475 g; prepared as described in Example 10 of UK Patent 2 202 847B) as starting material in place of N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid,
10 trifluoroacetic acid salt. There was thus obtained tri-tert-butyl-N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamate (0.340 g), m.p. 114-116°C.

NMR Spectrum: (CD$_3$SOCD$_3$) 1.36 (m, 27H, C(CH$_3$)$_3$), 1.74-2.20 (m) and
15 2.42 (m obscured) (8H, β-CH$_2$ and γ-CH$_2$), 2.31 (s, 3H, quinazoline 2-CH$_3$), 2.44 (s, 3H, quinazoline 7-CH$_3$), 2.62, 2.82 (2 x s, 3H, N-CH$_3$), 3.15 (s, 1H, C≡CH), 4.26 (s, 2H, CH$_2$C≡C), 4.30 (m obscured, 1H, glu α-CH), 4.44, 4.79 (2 x dd, J$_1$ = 10.58 Hz, J$_2$ = 4.86 Hz, 1H, N-Me glu α-CH), 4.66 (s, 2H, quinazoline 6-CH$_2$), 6.81 (d, J = 8.95
20 Hz, 2H, 3',5'-ArH), 7.43 (s, 1H, quinazoline 8-H), 7.74 (d, J = 7.74 Hz, 3H, quinazoline 5-H and 2',6'-ArH), 8.22 (t, J = 7.44 Hz, 1H, glu NH), 12.00 (s, 1H, lactam NH).

Mass Spectrum: (ESI) m/e 802 (M+H)$^+$.

Elemental Analysis: Found C, 65.37; H, 7.35; N, 8.63%.
25 C$_{44}$H$_{59}$N$_5$O$_9$·0.25H$_2$O requires: C, 65.53; H, 7.43; N, 8.68%.

A solution of tri-tert-butyl-N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamate (0.200 g) in trifluoroacetic acid (15 ml) was stirred for 1.2 hours at room temperature in the dark.
30 The solution was then concentrated in vacuo and the residue triturated with dry diethyl ether (20 ml). The white solid was isolated by filtration, washed with diethyl ether and dried in vacuo. There was thus obtained N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl-L-γ-
35 glutamyl-N-methyl-L-glutamic acid (0.180 g), m.p. 170°C decomp.

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NMR Spectrum: (CD_3SOCD_3) 1.82-2.23 (m) and 2.46 (m obscured)
(8H, β-CH_2 and γ-CH_2), 2.23, 2.48 (2 x s, 6H, quinazoline 2-CH_3 and
quinazoline 7-CH_3), 2.65, 2.81 (2 x s, 3H, N-CH_3), 3.23 (s, 1H,
C≡CH), 4.31 (m, 3H, CH_2C≡C and glu α-CH), 4.56, 4.91 (2 x dd,
05   J_1 = 10.87 Hz, J_2 = 4.38 Hz, 1H, N-Me glu α-CH), 4.71 (s, 2H,
quinazoline 6-CH_2), 6.79 (d, J = 8.89 Hz, 2H, 3',5'-ArH), 7.48 (s,
1H, quinazoline 8-H), 7.76 (m, 3H, 2',6'-ArH and quinazoline 5-H),
8.33 (m, 1H, glu NH).
Mass Spectrum (ESI) m/e 634 (M+H)$^+$.
10   Elemental Analysis: Found C, 53.23;   H, 5.00;   N, 8.86;   F, 7.33%.
$C_{32}H_{35}N_5O_9$·1CF_3COOH·1H_2O requires: C, 53.33;   H, 5.00;   N, 9.15;
F, 7.44%.

Example 8 : N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-
15   N-methyl-L-glutamic acid.

The process described in Example 1(3) was repeated using
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]-o-fluorobenzoic acid, trifluoroacetic acid salt
(0.479 g;   prepared as described in Example 6 of UK Patent
20   Application 2 253 849A) as starting material in place of
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid salt.
There was thus obtained tri-tert-butyl-N-p-[N-(3,4-dihydro-2-
methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-
25   fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamate (0.430 g),
m.p. 110-112°C.
NMR Spectrum: (CD_3SOCD_3) 1.36 (m, 27H, C(CH_3)$_3$), 1.80-2.20,
2.42 (2 x m, 8H, β-CH_2 and γ-CH_2), 2.33 (s, 3H, quinazoline 2-CH_3),
2.60, 2.80 (2 x s, 3H, N-CH_3), 3.27 (s, 1H, C≡CH), 4.29 (m, 1H, glu
30   α-CH), 4.37 (s, 2H, CH_2C≡C), 4.50 (dd) and 4.81 (dd obscured), (1H,
J_1 = 10.15 Hz, J_2 = 4.78 Hz, N-Me glu α-CH), 4.79 (s, 2H,
quinazoline 6-CH_2), 6.61 (d, J = 14.56 Hz, 1H, 3'-ArH), 6.66 (d,
J = 8.63 Hz, 1H, 5'-ArH), 7.52 (m, 2H, 6'-ArH and quinazoline 8-H),

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7.68 (dd, J_1 = 8.41 Hz, J_2 = 1.81 Hz, 1H, quinazoline 7-H),
7.95 (s, 1H, quinazoline 5-H), 8.02 (dd obscured) and 8.07 (dd)
(1H, J_1 = 7.04 Hz, J_2 = 4.2 Hz, glu NH), 12.21 (s, 1H, lactam NH).
Mass Spectrum: (ESI) m/e 806 (M+H)$^+$.

05   Elemental Analysis: Found C, 63.68; H, 6.97; N, 8.62; F, 2.54%.
$C_{43}H_{56}FN_5O_9 \cdot 0.25H_2O$ requires: C, 63.73; H, 7.03; N, 8.64;
F, 2.34%.

A solution of tri-_tert_-butyl-N-p-[N-(3,4-dihydro-2-methyl-
4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-

10   L-γ-glutamyl-N-methyl glutamate (0.220 g) in trifluoroacetic acid
(15 ml) was stirred for 1.2 hours at room temperature in the dark.
The solution was then concentrated _in vacuo_ and the residue
triturated with dry diethyl ether (20 ml). The white solid was
isolated by filtration, washed with diethyl ether and dried

15   _in vacuo_. There was thus obtained N-p-[N-(3,4-dihydro-2-methyl-
4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-
L-γ-glutamyl-N-methyl-L-glutamic acid (0.213 g), m.p. 120°C decomp.
NMR Spectrum: (CD$_3$SOCD$_3$) 1.82-2.20 (m) and 2.41 (m obscured)
(8H, β-CH$_2$ and γ-CH$_2$), 2.43 (s, 3H, quinazoline 2-CH$_3$), 2.63,

20   2.80 (2 x s, 3H, N-CH$_3$), 3.27 (s, 1H, C≡CH), 4.37 (m, 3H, CH$_2$C≡C
and glu α-CH), 4.54, 4.90 (2 x dd, J_1 = 11.23 Hz, J_2 = 4.35 Hz, 1H,
N-Me glu α-CH), 4.82 (s, 2H, quinazoline 6-CH$_2$), 6.61 (d,
J = 15.01 Hz, 1H, 3'-ArH), 6.66 (d, J = 8.10 Hz, 1H, 5'-ArH),
7.52 (t, J = 8.73 Hz, 1H, 6'-ArH), 7.61 (d, J = 8.42 Hz, 1H,

25   quinazoline 8-H), 7.77 (d, J = 8.48 Hz, 1H, quinazoline 7-H),
8.00 (s, 1H, quinazoline 5-H), 8.05 (m, 1H, glu NH).
Mass Spectrum: (ESI) m/e 638 (M+H)$^+$.
Elemental Analysis: Found C, 50.45; H, 4.65; N, 8.22; F, 11.12%.
$C_{31}H_{32}FN_5O_9 \cdot 1.3\ CF_3COOH \cdot 1H_2O \cdot 1Et_2O$ requires: C, 50.47; H, 4.59;

30   N, 8.55; F, 11.37%.

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Example 9 : N-p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid.

The process described in Example 1(3) was repeated using
05   N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoic acid, trifluoroacetic acid salt
(0.494 g; prepared as described in Example 7 of UK Patent
Application 2 253 849A) as starting material in place of
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
10   N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid salt.
There was thus obtained tri-tert-butyl-N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamate (0.400 g),
m.p. 122-124°C.
15   NMR Spectrum: (CD$_3$SOCD$_3$) 1.35 (m, 27H, C(CH$_3$)$_3$), 1.70-2.20 (m) and
2.40 (m obscured) (8H, β-CH$_2$ and γ-CH$_2$), 2.30 (s, 3H, quinazoline
2-CH$_3$), 2.43 (s, 3H, quinazoline 7-CH$_3$), 2.60, 2.80 (2 x s, 3H,
N-CH$_3$), 3.25 (s, 1H, C≡CH), 4.30 (m, 3H, CH$_2$C≡C and glu α-CH),
4.50, 4.79 (2 x dd, J$_1$ = 10.68 Hz, J$_2$ = 4.61 Hz, 1H, N-Me glu
20   α-CH), 4.68 (s, 2H, quinazoline 6-CH$_2$), 6.61 (m, 2H, 3',5'-ArH),
7.44 (s, 1H, quinazoline 8-H), 7.51 (t, J = 8.67 Hz, 1H, 6'-ArH),
7.68 (s, 1H, quinazoline 5-H), 8.00, 8.08 (2 x dd, J$_1$ = 6.98 Hz,
J$_2$ = 4.30 Hz, 1H, glu NH), 12.10 (s, 1H, lactam NH).
Mass Spectrum: (ESI) m/e 820 (M+H)$^+$.
25   Elemental Analysis: Found C, 64.25; H, 7.10; N, 8.51; F, 2.36%.
C$_{44}$H$_{58}$FN$_5$O$_9$ requires: C, 64.45; H, 7.13; N, 8.54; F, 2.32%.
A solution of tri-tert-butyl-N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl glutamate (0.215 g) in trifluoroacetic acid
30   (16 ml) was stirred for 1.2 hours at room temperature in the dark.

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The solution was then concentrated in vacuo and the residue
triturated with dry diethyl ether (20 ml). The white solid was
isolated by filtration, washed with diethyl ether and dried
in vacuo. There was thus obtained N-p-[N-(3,4-dihydro-2,7-dimethyl-
05   4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-o-fluorobenzoyl-
L-γ-glutamyl-N-methyl-L-glutamic acid (0.205 g), m.p. 150°C decomp.
NMR Spectrum: (CD_3SOCD_3) 1.82-2.20 (m) and 2.46 (m obscured)
(8H, β-CH_2 and γ-CH_2), 2.45, 2.48 (2 x s, 6H, quinazoline 2-CH_3 and
quinazoline 7-CH_3), 2.63, 2.81 (2 x s, 3H, N-CH_3), 3.25 (s, 1H,
10   C≡CH), 4.33 (m, 3H, CH_2C≡C and glu α-CH), 4.58, 4.90 (2 x dd,
J_1 = 10.94 Hz, J_2 = 4.43 Hz, 1H, N-Me glu α-CH), 4.74 (s, 2H,
quinazoline 6-CH_2), 6.61 (m, 2H, 3',5'-ArH), 7.49 (s, 1H,
quinazoline 8-H), 7.54 (t, J = 8.73 Hz, 1H, 6'-ArH), 7.73 (s, 1H,
quinazoline 5-H), 8.08 (m, 1H, glu NH).
15   Mass Spectrum: (ESI) m/e 652 (M+H)$^+$.
Elemental Analysis: Found C, 50.90; H, 4.52; N, 8.40; F, 11.58%.
$C_{32}H_{34}FN_5O_9 \cdot 1.3$ $CF_3COOH \cdot 1H_2O$ requires: C, 50.81; H, 4.60;
N, 8.56; F, 11.38%.

Example 10 : N-p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxoquinazolin-6-
20   ylmethyl)-N-methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic
acid.

The process described in Example 1(3) was repeated using
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoic acid, trifluoroacetic acid salt (0.450 g;
25   prepared as described in Example 11 of UK Patent
Application 2 253 849A) as starting material in place of
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-
N-(prop-2-ynyl)amino]benzoic acid, trifluoroacetic acid salt.
There was thus obtained tri-tert-butyl-N-p-[N-(3,4-dihydro-2,7-
30   dimethyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]benzoyl-L-γ-
glutamyl-N-methyl-L-glutamate (0.260 g), m.p. 139-140°C.

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NMR Spectrum: (CD$_3$SOCD$_3$) 1.35 (m, 27H, C(CH$_3$)$_3$), 1.80-2.18 (m) and
2.40 (m obscured) (8H, β-CH$_2$ and γ-CH$_2$), 2.30 (s, 3H, quinazoline
2-CH$_3$), 2.43 (s, 3H, quinazoline 7-CH$_3$), 2.61, 2.81 (2 x s, 3H,
N-CH$_3$), 3.13 (s, 3H, 10-N-CH$_3$), 4.25 (m, 1H, glu α-CH), 4.69 (s,
05   2H, quinazoline 6-CH$_2$), 4.48, 4.80 (2 x dd, J$_1$ = 10.72 Hz,
J$_2$ = 4.66 Hz, 1H, N-Me glu α-CH), 6.70 (d, J = 8.88 Hz, 2H,
3',5'-ArH), 7.44, 7.53 (2 x s, 2H, quinazoline 5-H and
quinazoline 8-H), 7.71 (d, J = 8.77 Hz, 2H, 2',6'-ArH),
8.24 (t, J = 7.51 Hz, 1H, glu NH), 12.10 (s, 1H, lactam NH).
10   Mass Spectrum: (ESI) m/e 778 (M+H)$^+$.
Elemental Analysis: Found C, 64.32; H, 7.58; N, 8.92%.
C$_{42}$H$_{59}$N$_5$O$_9$·0.3H$_2$O requires: C, 64.40; H, 7.67; N, 8.94%.
      Tri-tert-butyl-N-p-[N-(3,4-dihydro-2,7-dimethyl-4-
oxoquinazolin-6-ylmethyl)-N-methylamino]benzoyl-L-γ-glutamyl-
15   N-methyl-L-glutamate (0.135 g) in trifluoroacetic acid (12 ml) was
stirred for 1.2 hours at room temperature in the dark. The
solution was then concentrated in vacuo and the residue triturated
with dry diethyl ether and dried in vacuo. There was thus obtained
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
20   methylamino]-benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid
(0.120 g), m.p. 155°C decomp.
NMR Spectrum: (CD$_3$SOCD$_3$) 1.80-2.16 (m) and 2.41 (m obscured)
(8H, β-CH$_2$ and γ-CH$_2$), 2.40, 2.47 (2 x s, 6H, quinazoline 2-CH$_3$ and
quinazoline 7-CH$_3$), 2.64, 2.80 (2 x s, 3H, N-CH$_3$), 3.13 (s, 3H,
25   10-N-CH$_3$), 4.31 (m, 1H, glu α-CH), 4.57, 4.91 (2 x dd, J$_1$ = 11.0 Hz,
J$_2$ = 4.31 Hz, 1H, N-Me glu α-CH), 4.72 (s, 2H, quinazoline 6-CH$_2$),
6.71 (d, J = 8.71 Hz, 2H, 3',5'-ArH), 7.47, 7.53 (2 x s, 2H,
quinazoline 5-H and quinazoline 8-H), 7.73 (d, J = 8.53 Hz, 2H,
2',6'-ArH), 8.28 (d, J = 7.18 Hz, H, glu NH).
30   Mass Spectrum: (ESI) m/e 610 (M+H)$^+$.
Elemental Analysis: Found C, 51.29; H, 5.14; N, 9.00; F, 7.73%.
C$_{30}$H$_{35}$N$_5$O$_9$·1CF$_3$COOH·1.5 H$_2$O requires: C, 51.20; H, 5.24;
N, 9.33; F, 7.59%.

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Example 11 : N-p-[N-(3,4-Dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-
L-glutamic acid.

The process described in Example 1(3) was repeated using

05   N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoic acid, trifluoroacetic acid salt
(0.410 g; prepared as described in Example 12 of UK Patent
Application 2 253 849A) in place of N-p-[N-(3,4-dihydro-2-methyl-
4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid,

10   trifluoroacetic acid salt. There was thus obtained tri-tert-butyl-
N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-
o-fluorobenzoyl-L-γ-glutamyl- N-methyl-L-glutamate (0.465 g),
m.p. 107-109°C.

NMR Spectrum: (CD₃SOCD₃) 1.35 (m, 27H, C(CH₃)₃), 1.80-2.18,

15   2.42 (2 x m, 8H, β-CH₂ and γ-CH₂), 2.32 (s, 3H, quinazoline 2-CH₃),
2.60, 2.80 (2 x s, 3H, N-CH₃), 3.13 (s, 3H, 10-N-CH₃), 4.29 (m, 1H,
glu α-CH), 4.49 (m) and 4.79 (m obscured) (1H, N-Me glu α-CH),
4.78 (s, 2H, quinazoline 6-CH₂), 6.54 (d, J = 16.11 Hz, 1H,
3'-ArH), 6.61 (d, 9.33 Hz, 1H, 5'-ArH), 7.56 (m, 3H, 6'-ArH,

20   quinazoline 7-H and quinazoline 8-H), 7.84 (s, 1H, quinazoline
5-H), 7.87, 7.97 (2 x t, J = 6.20 Hz, 1H, glu NH), 12.22 (s, 1H,
lactam NH).

Mass Spectrum: (ESI) m/e 782 (M+H)⁺.

Elemental Analysis: Found C, 62.70; H, 7.21; N, 9.02; F, 2.62%.

25   C₄₁H₅₆N₅O₉F requires: C, 62.98; H, 7.22; N, 8.96; F, 2.43%.

Tri-tert-butyl-N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-
ylmethyl)-N-methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-
glutamate (0.295 g) in trifluoroacetic acid (23 ml) was stirred
for 1.2 hours at room temperature in the dark. The solution was

30   then concentrated in vacuo and the residue triturated with dry
diethyl ether and dried in vacuo. There was thus obtained
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid
(0.270 g), m.p. 110°C decomp.

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NMR Spectrum: (CD₃SOCD₃) 1.82-2.18 (m) and 2.40 (m obscured)
(8H, β-CH₂ and γ-CH₂), 2.45 (s, 3H, quinazoline 2-CH₃), 2.63,
2.81 (2 x s, 3H, N-CH₃), 3.13 (s, 3H, 10-N-CH₃), 4.34 (m, 1H,
glu α-CH), 4.53, 4.90 (2 x dd, J₁ = 10.91 Hz, J₂ = 4.36 Hz, 1H,
05   N-Me glu α-CH), 4.83 (s, 2H, quinazoline 6-CH₂), 6.56 (d,
J = 15.86 Hz, 1H, 3'-ArH), 6.62 (d, J = 9.1 Hz, 1H, 5'-ArH),
7.53 (t, J = 9.02 Hz, 1H, 6'-ArH), 7.62 (d, J = 8.43 Hz, 1H,
quinazoline 8-H), 7.70 (dd, J₁ = 8.43 Hz, J₂ = 1.82 Hz, 1H,
quinazoline 7-H), 7.89 (d, J = 1.52 Hz, 1H, quinazoline 5-H),
10   7.97 (t, J = 5.50 Hz, glu NH).
Mass Spectrum: (ESI) m/e 614 (M+H)⁺.
Elemental Analysis: Found C, 48.32; H, 4.72; N, 8.12; F, 13.16%.
C₂₉H₃₂FN₅O₉·1.6CF₃COOH·0.4Et₂O H₂O requires: C, 48.12; H, 4.73;
N, 8.30; F, 13.05%.

15   Example 12 : N-p-[N-(3,4-Dihydro-2,7-dimethyl-4-oxoquinazolin-6-
ylmethyl)-N-methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-
L-glutamic acid.

The process described in Example 1(3) was repeated using
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
20   methylamino]-o-fluorobenzoic acid, trifluoroacetic acid salt
(0.478 g; prepared as described in Example 13 of UK Patent
Application 2 253 849A) in place of N-p-[N-(3,4-dihydro-2-methyl-4-
oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoic acid,
trifluoroacetic acid salt. There was thus obtained tri-tert-butyl-
25   N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-
N-methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamate
(0.518 g), m.p. 162-164°C.
NMR Spectrum: (CD₃SOCD₃) 1.36 (m, 27H, C(CH₃)₃), 1.73-2.18 (m)
and 2.40 (m obscured) (8H, β-CH₂ and γ-CH₂), 2.30 (s, 3H,
30   quinazoline 2-CH₃), 2.42 (s, 3H, quinazoline 7-CH₃), 2.60,
2.80 (2 x s, 3H, N-CH₃), 3.11 (s, 3H, 10-N-CH₃), 4.29 (m, 1H,
glu α-CH), 4.50, 4.79 (2 x dd, J₁ = 10.72 Hz, J₂ = 4.53 Hz, 1H,
N-Me glu α-CH), 4.69 (s, 2H, quinazoline 6-CH₂), 6.51 (d,
J = 14.38 Hz, 1H, 3'-ArH), 6.56 (d, J = 8.10 Hz, 1H, 5'-ArH),

7.48 (m, 3H, 6'-ArH, quinazoline 5-H and quinazoline 8-H), 7.88,
7.98 (2 x t, J = 6.13 Hz, 1H, glu NH), 12.12 (s, 1H, lactam NH).
Mass Spectrum: (ESI) m/e 796 (M+H)$^{+}$.
Elemental Analysis: Found C, 63.19; H, 7.31; N, 8.80; F, 2.44%.
05    $C_{42}H_{58}N_5O_9F$ requires: C, 63.38; H, 7.34; N, 8.80; F, 2.39%.

      Tri-_tert_-butyl-_N_-_p_-[_N_-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-
6-ylmethyl)-_N_-methylamino]-_o_-fluorobenzoyl-L-γ-glutamyl-_N_-methyl-
glutamate (0.296 g) was treated with trifluoroacetic acid (23 ml)
and stirred for 1.2 hours at room temperature in the dark. The
10   solution was then concentrated _in vacuo_ and the residue triturated
with dry diethyl ether and dried _in vacuo_. There was thus obtained
_N_-_p_-[_N_-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-_N_-
methylamino]-_o_-fluorobenzoyl-L-γ-glutamyl-_N_-methyl-L-glutamic acid
(0.285 g), m.p. 155°C decomp.
15   NMR Spectrum: (CD_3SOCD_3) 1.80-2.18 (m) and 2.40 (m obscured)
(8H, β-CH_2 and γ-CH_2), 2.43, 2.47 (2 x s, 6H, quinazoline 2-CH_3 and
quinazoline 7-CH_3), 2.63, 2.81 (2 x s, 3H, N-CH_3), 3.13 (s, 3H,
10-N-CH_3), 4.34 (m, 1H, glu$_L$ α-CH), 4.54, 4.90 (2 x dd,
J_1 = 10.98 Hz, J_2 = 4.43 Hz, 1H, N-Me glu α-CH), 4.73 (s, 2H,
20   quinazoline 6-CH_2), 6.53 (d, J = 13.10 Hz, 1H, 3'-ArH), 6.57 (d,
J = 6.90 Hz, 1H, 5'-ArH), 7.48, 7.50 (2 x s, 2H, quinazoline 5-H
and quinazoline 8-H), 7.54 (t obscured), J = 9.30 Hz, 1H, 6'-ArH),
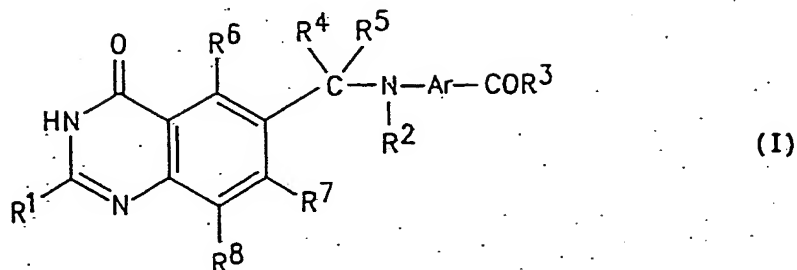7.09 (m, 1H, glu NH).
Mass Spectrum: (ESI) m/e 628 (M+H)$^{+}$.
25   Elemental Analysis: Found C, 49.73; H, 5.01; N, 8.16; F, 11.50%.
$C_{30}H_{34}FN_5O_9$·1.4CF_3COOH·0.5Et_2O.1H_2O requires: C, 49.62; H, 5.07;
N, 8.31; F, 11.72%.

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CLAIMS

1. A quinazoline of the formula (I):-

(I)

wherein R^1 is hydrogen or amino;

or R^1 is alkyl, alkoxy or alkylthio each of up to 6 carbon atoms;

or R^1 is aryl or aryloxy, each of up to 10 carbon atoms;

05   or R^1 is halogeno, hydroxy or mercapto;

or R^1 is alkyl of up to 3 carbon atoms which bears one or more

substituents selected from halogeno, hydroxy and alkanoylamino each

of up to 6 carbon atoms;

or R^1 is alkoxy of up to 3 carbon atoms which bears one or more

ა   substituents selected from hydroxy and alkoxy of up to 6 carbon

atoms;

wherein R^2 is hydrogen or alkyl, alkenyl, alkynyl, hydroxyalkyl,

alkoxyalkyl, mercaptoalkyl, alkylthioalkyl, halogenoalkyl,

cyanoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,

15   alkanoylalkyl, carboxyalkyl, carbamoylalkyl or alkanoyl each of up

to 6 carbon atoms;

wherein Ar is phenylene or heterocyclene which is unsubstituted or

which bears one or more substituents selected from halogeno, cyano,

nitro, hydroxy, amino and carbamoyl and alkyl, alkoxy,

20   halogenoalkyl, alkanoylamino and alkoxycarbonyl each of up to 6

carbon atoms;

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wherein R^3 is the residue of a dipeptide in which the first,
N-terminal amino acid residue thereof attached to the carbonyl
group of COR^3

$$V$$
is an amino acid residue $-NHCH(CO_2H)-A-\overset{V}{\underset{V'}{C}}-CO-$ in which A is a

05   carbon-carbon single bond or an alkylene group of up to 5 carbon
atoms and V and V' are each separately hydrogen, or alkyl, alkenyl
or alkynyl each of up to 6 carbon atoms; and the second amino acid
residue is of an α-amino acid but with one or more of the following
provisos:

10   (a) at least one of V and V' is other than hydrogen;
(b) the nitrogen atom of the second amino acid residue is
substituted by an alkyl, alkenyl or alkynyl group of up to 4 carbon
atoms, by an alkyl group of up to 3 carbon atoms which bears one or
more halogeno group substituents or a hydroxy group substituent, or

15   by an ethylene, trimethylene or tetramethylene group linked to the
α-carbon atom of the second amino acid residue, and
(c) the α-carbon atom of the second amino acid residue is fully
substituted;
wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms;

20   wherein R^5 is hydrogen or alkyl of up to 4 carbon atoms; and
wherein each of R^6, R^7 and R^8 is hydrogen or alkyl or alkoxy each
of up to 4 carbon atoms; or is halogeno; the quinazoline
optionally being in the form of a pharmaceutically acceptable salt,
ester or amide thereof.

25   2. A quinazoline according to Claim 1, wherein R^3 is the residue
of a dipeptide in which the first, N-terminal amino acid residue
thereof attached to the carbonyl group of COR^3 is an amino acid

$$V$$
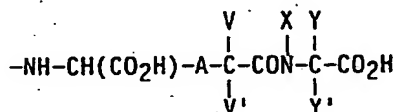residue $-NHCH(CO_2H)-A-\overset{V}{\underset{V'}{C}}-CO-$ in which A is a carbon-carbon single

bond or an alkylene group of up to 5 carbon atoms and, V and V' are
30   each separately hydrogen, or alkyl, alkenyl or alkynyl each of up
to 6 carbon atoms; and the second amino acid residue is of an
α-amino acid substituted on the nitrogen atom by an alkyl, alkenyl

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or alkynyl group of up to 4 carbon atoms, by an alkyl group of up
to 3 carbon atoms which bears one or more halogeno group
substituents or a hydroxy group substituent, or by an ethylene,
trimethylene or tetramethylene group linked to the α-carbon atom
05   thereof.

3. A quinazoline according to Claim 1, wherein R^3 is a group of
formula

$$-NH-CH(CO_2H)-A-\overset{\overset{\displaystyle V}{|}}{\underset{\underset{\displaystyle V'}{|}}{C}}-CON-\overset{\overset{\displaystyle Y}{|}}{\underset{\underset{\displaystyle Y'}{|}}{C}}-CO_2H$$

with X above the middle

in which A is a carbon-carbon single bond or an alkylene group of
10   up to 5 carbon atoms and V and V' are each separately hydrogen, or
alkyl, alkenyl or alkynyl each of up to 6 carbon atoms;

    X is hydrogen or alkyl, alkenyl or alkynyl each of up
to 4 carbon atoms;

    Y is hydrogen or alkyl, alkenyl or alkynyl each of up
15   to 6 carbon atoms;

    or X and Y together are a group $(CH_2)_n$ where n is 2, 3 or 4;

    and Y' is hydrogen or alkyl, alkenyl or alkynyl each of up to 6
carbon atoms;

    or Y' is alkyl of up to 6 carbon atoms which bears one or more
20   substituents selected from amino, carboxy, hydroxy and mercapto;

    or Y' is phenyl or benzyl; but with one or more of the
following provisos:

(a) at least one of V and V' is other than hydrogen,

(b) X is other than hydrogen, and

25   (c) Y and Y' are each other than hydrogen.

4. A quinazoline according to any of Claims 1 to 3, wherein
A-CV(V') is a group A' in which A' is an alkylene group of up
to 6 carbon atoms.

5. A quinazoline according to Claim 4, wherein A' is CH_2, CH_2CH_2,
30    $CH_2CH_2CH_2$, $CH(CH_3)CH_2$, $CH_2CH(CH_3)$ or $CH_2C(CH_3)_2$.

6. A quinazoline according to any of Claims 3 to 5, wherein X is
methyl or ethyl, or X and Y together form a group $(CH_2)_3$.

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7. A quinazoline according to any of Claims 3 to 6, wherein Y is hydrogen, methyl or ethyl, or X and Y together form a group $(CH_2)_3$.

8. A quinazoline according to Claim 3, wherein A-CV(V') is CH_2CH_2,
05   X is methyl and Y is hydrogen.

9. A quinazoline according to Claim 3, wherein R^3 is a group of the formula

$$-NH-CH(CO_2H)-CH_2CH_2-CON(CH_3)CH(CO_2H)-(CH_2)_mCO_2H$$

in which m is 1, 2 or 3.

10   10. A quinazoline according to any of the preceding claims, wherein R^1 is hydrogen, amino, methyl, ethyl, isopropyl, methoxy, ethoxy, methylthio, phenyl, tolyl, phenoxy, chloro, bromo, hydroxy, mercapto, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, acetamidomethyl, 2-hydroxyethoxy,
15   2-methoxyethoxy or 2-ethoxyethoxy;

wherein R^2 is hydrogen, methyl, ethyl, propyl, prop-2-enyl, but-2-enyl, prop-2-ynyl, but-2-ynyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-mercaptoethyl, 2-methylthioethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl,
20   3-fluoropropyl, cyanomethyl, 2-cyanoethyl, 2-aminoethyl, 2-methylaminoethyl, 2-dimethylaminoethyl, acetonyl, carboxymethyl, carbamoylmethyl or acetyl;

wherein Ar is 1,4-phenylene, thienylene, pyridylene, pyrimidinylene, thiazolylene or oxazolylene which is unsubstituted
25   or which bears one or two substituents selected from fluoro, chloro, bromo, phenyl, cyano, nitro, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy, fluoromethyl, difluoromethyl, trifluoromethyl or acetamido;

wherein R^4 is hydrogen, methyl or ethyl;
30   wherein R^5 is hydrogen, methyl or ethyl; and

wherein each of R^6, R^7 and R^8 is hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro or bromo.

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11. A quinazoline according to Claim 1, wherein R^1 is hydrogen,
amino, methyl, ethyl or methoxy;
wherein R^2 is methyl, ethyl, prop-2-enyl, prop-2-ynyl,
2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl or acetonyl;
05   wherein Ar is 1,4-phenylene, 2-fluoro-1,4-phenylene or
2,6-difluoro-1,4-phenylene;
wherein R^3 is a group of formula:-

$$-NH-CH(CO_2H)CH_2CH_2CON(CH_3)CH(CO_2H)-(CH_2)_mCO_2H$$

in which m is 1, 2 or 3;
10   wherein R^4 is hydrogen or methyl;
wherein R^5 is hydrogen;
wherein R^6 is hydrogen or chloro;
wherein R^7 is hydrogen, methyl, fluoro or chloro; and
wherein R^8 is hydrogen, methoxy or chloro.
15   12. A quinazoline according to Claim 1, wherein R^1 is amino,
methyl or methoxy;
wherein R^2 is methyl, ethyl, prop-2-enyl, prop-2-ynyl,
2-hydroxyethyl, 3-hydroxypropyl, 2-fluoroethyl or acetonyl;
wherein Ar is 1,4-phenylene, 2-fluoro-1,4-phenylene or
20   2,6-difluoro-1,4-phenylene;
wherein R^3 is the residue of the dipeptide γ-glutamyl-N-methyl-
2-aminoadipic acid or γ-glutamyl-N-methylglutamic acid;
wherein R^4 is hydrogen or methyl;
wherein R^5 is hydrogen;
25   wherein R^6 is hydrogen or chloro;
wherein R^7 is hydrogen, methyl, fluoro or chloro; and
wherein R^8 is hydrogen, methoxy or chloro.
13. A quinazoline according to any of the preceding claims,
wherein the first amino acid residue of the group R is of
30   the L configuration about the α-carbon atom thereof and the second
amino acid residue is also of the L configuration about the
α-carbon atom thereof when that atom is asymmetric.

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14. A quinazoline according to Claim 1 wherein R^1 is methyl;
wherein R^2 is methyl or prop-2-ynyl;
wherein Ar is 1,4-phenylene or 2-fluoro-1,4-phenylene;
wherein R^3 is the residue of L-γ-glutamyl-N-methyl-L-glutamic acid;
05   wherein R^4 is hydrogen or methyl;
wherein R^5 is hydrogen;
wherein R^6 is hydrogen or chloro;
wherein R^7 is hydrogen, methyl, methoxy, fluoro or chloro; and
wherein R^8 is hydrogen, methyl, methoxy or chloro.

10   15. A compound being:
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
15   N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
20   ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
25   N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
30   methylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid; or

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N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]benzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid;
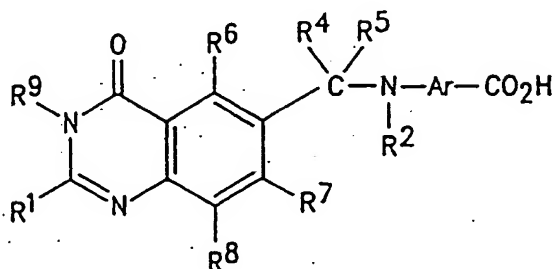or a pharmaceutically acceptable salt, ester or amide thereof.

16. A compound being:

05   N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-amino-4-oxoquinazolin-6-ylmethyl)-N-(prop-

10   2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,

15   N-p-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-
2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-

20   ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2,7-dimethyl-4-oxoquinazolin-6-ylmethyl)-N-
(prop-2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic
acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-

25   methylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-
ethylamino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid,
or
N-p-[N-(3,4-dihydro-2-methoxy-4-oxoquinazolin-6-ylmethyl)-N-(prop-

30   2-ynyl)amino]-o-fluorobenzoyl-L-γ-glutamyl-N-methyl-L-glutamic acid;
or a pharmaceutically acceptable salt, ester or amide thereof.

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17. A process for the manufacture of a quinazoline according to
Claim 1 which comprises:-

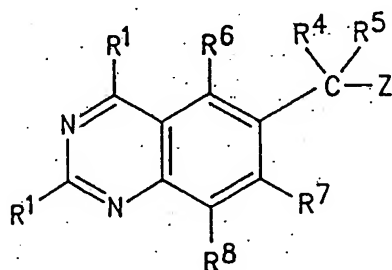(a) the reaction of an acid of the formula:-

$$R^9-N \quad \overset{O}{\underset{\parallel}{C}} \quad R^6 \quad R^4 \quad R^5$$
$$\overset{|}{\underset{R^1}{N}} \quad \overset{|}{\underset{N}{\quad}} \quad R^7 \quad \overset{|}{\underset{R^2}{C}}-N-Ar-CO_2H$$
$$R^8$$

or a reactive derivative thereof,

05   with a compound having a terminal amino group of the formula R^3–H
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Ar have the meanings
stated in Claim 1 and any mercapto, amino and alkylamino group in
R^1, R^2, R^3 and Ar and any carboxy group in R^1, R^2 and Ar is
protected by a conventional protecting group, and any hydroxy group

10   in R^1, R^2, R^3 and Ar and any carboxy group in R^3 may be protected
by a conventional protecting group or alternatively such a hydroxy
or carboxy group need not be protected;

wherein R^9 is hydrogen or a protecting group;

(b) when the quinazoline has a group R^1 which is alkoxy, aryloxy or

15   alkoxy of up to 3 carbon atoms which bears one or more substituents
selected from hydroxy and alkoxy of up to 6 carbon atoms, the
reaction of a compound of the formula:

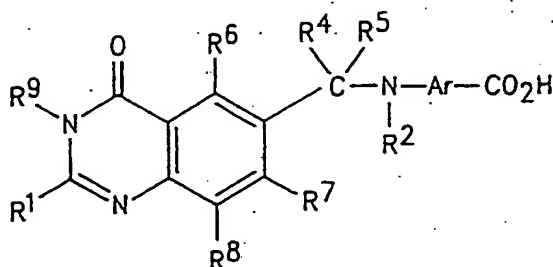$$R^1 \quad R^6 \quad R^4 \quad R^5$$
$$\underset{N}{\quad} \quad \underset{}{\quad} \quad \overset{|}{\underset{}{C}}-Z$$
$$\underset{R^1}{\quad} \overset{}{\underset{N}{\quad}} \quad R^7$$
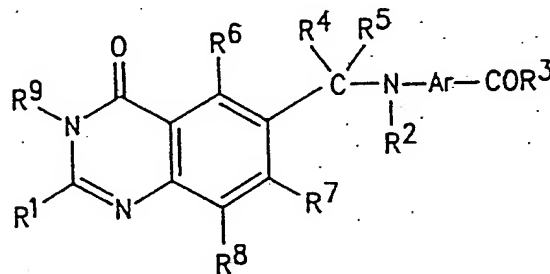$$R^8$$

with a compound of the formula:

$$HNR^2-Ar-COR^3$$

wherein R^1 has the meaning just stated under (b) above;

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Ar have the meanings stated under (a) above, provided that any mercapto, amino, alkylamino and carboxy group in R^2, R^3 and Ar is protected by a conventional

05   protecting group and any hydroxy group in R^1, R^2, R^3 and Ar may be protected by a conventional protecting group or alternatively any hydroxy group need not be protected;

and Z is a displaceable group;

(c) when the quinazoline has a group R^1 which is mercapto or

10   alkylthio the reaction of a quinazoline of the formula:-

wherein R^1 is halogeno or halogenoalkyl;

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and Ar have the meanings stated under (a) above provided that any mercapto, amino, alkylamino, carboxy and hydroxy group in R^2, R^3 and Ar may be

15   protected by a conventional protecting group or alternatively any amino, alkylamino, carboxy and hydroxy group need not be protected; with thiourea to provide a compound wherein R^1 is mercapto; or with an alkyl thiol to provide a compound wherein R^1 is alkylthio; whereafter the protecting groups are removed by conventional means;

20   (d) when the quinazoline has a group R^1 which is alkylthio, the reaction of a quinazoline of the formula:-

wherein R^1 is mercapto;

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and Ar have the meanings stated under (a) above, provided that any mercapto, amino, alkylamino, carboxy and hydroxy group in R^2, R^3 and Ar may be
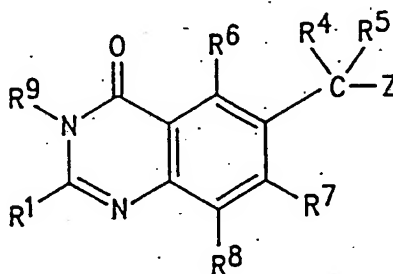05　protected by a conventional protecting group or alternatively any amino, alkylamino, carboxy and hydroxy group need not be protected; with a base, followed by alkylation of the resultant thiolate salt with an alkyl halide; or

(e) the reaction of a compound of the formula:-

10　with a compound of the formula:-

$$HNR^2-Ar-COR^3$$

where within these compounds R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and Ar have the meanings stated under (a) above, provided that when there is a hydroxy group in R^1, R^3 or Ar, when there is a
15　hydroxyalkyl group in R^1 or R^2, when there is a hydroxyalkoxy group in R^1, when there is an amino group in R^1, R^3 or Ar, when there is an aminoalkyl group in R^2, when there is an alkylaminoalkyl group in R^2, when there is a carboxy or carboxyalkyl group in R^2 or R^3 or when there is a mercapto or mercaptoalkyl group in R^1, R^2 or R^3 any
20　amino, carboxy and mercapto group is protected by a conventional protecting group and any hydroxy group may be protected by a conventional protecting group or alternatively any hydroxy group need not be protected;

and Z is a displaceable group;

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and thereafter, where appropriate, in any of (a) to (e), any
undesired protecting group, including any protecting group R^9, is
removed by conventional means and, in (b), the R^1 group situated at
the 4-position of the quinazoline ring is cleaved by hydrolysis
05   with a base and/or in any of (a) to (e) the compound of formula (I)
is converted to a pharmaceutically acceptable salt, ester or amide
thereof.

18. A pharmaceutical composition comprising a quinazoline
according to any of Claims 1 to 16 together with a pharmaceutically
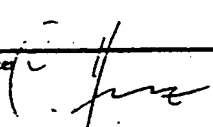10   acceptable diluent or carrier.

19. The use of a quinazoline according to any of Claims 1 to 16
for the manufacture of a medicament for use in the treatment of
cancer.

20. A method for aiding regression and palliation of cancer in a
15   patient in need of such treatment which comprises administering to
said patient an effective amount of a quinazoline according to any
of Claims 1 to 16.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)°

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D239/95;　　C07D239/90;　　C07D239/96;　　A61K31/505

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ;　A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category°	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,Y	EP,A,0 509 643 (BRITISH TECHNOLOGY GROUP LTD & IMPERIAL CHEMICAL INDUSTRIES PLC) 21 October 1992 see claims 1-12	1-20
Y	EP,A,0 239 362 (IMPERIAL CHEMICAL INDUSTRIES PLC & NATIONAL RESEARCH DEVELOPMENT CORP.) 30 September 1987 cited in the application see claims 1-10	1-20
Y	EP,A,0 204 529 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 10 December 1986 cited in the application see claims 1-22	1-20

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 MAY 1993	-7. 06. 93

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	HERZ C.P.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT	**(CONTINUED FROM THE SECOND SHEET)**	
Category°	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0 031 237 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 1 July 1981 cited in the application see claims 1-23 -----	1-20

INTERNATIONAL SEARCH REPORT

Box I   Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   The definition of substituent A as being "heterocyclene" is too general
   and encompasses too broad a range of totally different chemical groups not
   supported by the specification. The vast number of theoretically con-
   ceivable compounds precludes a comprehensive search.

3. ☐ Claims searched incompletely: 1 - 9, 13, 17 - 19
   Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II   Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300540
SA 71439

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.   10/05/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0509643	21-10-92	AU-A-	1371692	21-10-92
		WO-A-	9216512	01-10-92
		GB-A-	2253849	23-09-92
EP-A-0239362	30-09-87	AU-B-	592628	18-01-90
		AU-A-	7047287	01-10-87
		DE-A-	3774909	16-01-92
		GB-A,B	2188319	30-09-87
		JP-A-	1125373	17-05-89
		US-A-	4992550	12-02-91
		US-A-	5081124	14-01-92
		US-A-	5187167	16-02-93
EP-A-0204529	10-12-86	AU-B-	592271	04-01-90
		AU-A-	5822086	04-12-86
		GB-A,B	2175903	10-12-86
		JP-A-	61282368	12-12-86
EP-A-0031237	01-07-81	AT-T-	9900	15-11-84
		AU-B-	543237	04-04-85
		AU-A-	6549580	25-06-81
		CA-A-	1184900	02-04-85
		GB-A,B	2065653	01-07-81
		JP-B-	5012347	17-02-93
		JP-A-	56092876	27-07-81
		US-A-	4447608	08-05-84
		US-A-	4564616	14-01-86

EPO FORM P0479